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# UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No. AR 218-X Total Pages 88

First Named Inventor or Application Identifier

Gregory S. Hamilton

Express Mail Label No.

**APPLICATION ELEMENTS**  
 See MPEP chapter 600 concerning utility patent application contents.
ADDRESS TO: Assistant Commissioner for Patents  
Box Patent Application  
Washington, DC 20231

1.  Fee Transmittal Form  
(Submit an original, and a duplicate for fee processing)
2.  Specification [Total Pages 85]  
(preferred arrangement set forth below)
  - Descriptive title of the Invention
  - Cross References to Related Applications
  - Statement Regarding Fed sponsored R & D
  - Reference to Microfiche Appendix
  - Background of the Invention
  - Brief Summary of the Invention
  - Brief Description of the Drawings (if filed)
  - Detailed Description
  - Claim(s)
  - Abstract of the Disclosure
3.  Drawing(s) (35 USC 113) [Total Sheets 3]
4. Oath or Declaration [Total Pages 2]
  - a.  Newly executed (original or copy)
  - b.  Copy from a prior application (37 CFR 1.63(d))  
(for continuation/divisional with Box 17 completed)  
[Note Box 5 below]
    - i.  DELETION OF INVENTOR(S)  
Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
5.  Incorporation By Reference (useable if Box 4b is checked)  
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6.  Microfiche Computer Program (Appendix)
7. Nucleotide and/or Amino Acid Sequence Submission  
(if applicable, all necessary)
  - a.  Computer Readable Copy
  - b.  Paper Copy (identical to computer copy)
  - c.  Statement verifying identity of above copies

**ACCOMPANYING APPLICATION PARTS**

8.  Assignment Papers (cover sheet & document(s))
9.  37 CFR 3.73(b) Statement  Power of Attorney  
(when there is an assignee)
10.  English Translation Document (if applicable)
11.  Information Disclosure Statement (IDS)/PTO-1449  Copies of IDS Citations
12.  Preliminary Amendment
13.  Return Receipt Postcard (MPEP 503)  
(Should be specifically itemized)
14.  Small Entity  Statement filed in prior application, Statement(s)  Status still proper and desired
15.  Certified Copy of Priority Document(s)  
(if foreign priority is claimed)
16.  Other: .....

## 17. If a CONTINUING APPLICATION, check appropriate box and supply the requisite information:

 Continuation    Divisional    Continuation-in-part (CIP)

of prior application No: 60,087,842

**18. CORRESPONDENCE ADDRESS** Customer Number or Bar Code Labelor  Correspondence address below

(Insert Customer No. or Attach bar code label here)

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Title:

N-LINKED SULFONAMIDES OF  
N-HETEROCYCLIC CARBOXYLIC ACIDS OR CARBOXYLIC ACID ISOSTERES

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N-Linked Sulfonamides of  
N-Heterocyclic Carboxylic Acids or  
Carboxylic Acid Isosteres

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Related Application Data

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This application is a continuation-in-part of U.S. patent application serial number 60/087,842 to Hamilton et al., entitled "N-Linked Sulfonamides of N-Heterocyclic Carboxylic Acids and Carboxylic Acid Isosteres", filed June 3, 1998.

PCT/US2002/015529

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BACKGROUND OF THE INVENTION

**1. Field of the Invention**

This invention relates to small molecule compounds and compositions, their preparation and use for treating neurological disorders including physically damaged nerves and neurodegenerative diseases, and for treating alopecia and promoting hair growth.

**2. Description of the Prior Art**

It has been found that picomolar concentrations of an immunosuppressant such as FK506 and rapamycin stimulate neurite outgrowth in PC12 cells and sensory nervous, namely dorsal root ganglion cells (DRGs). Lyons et al., *Proc. of Natl. Acad. Sci.*, 1994 vol. 91, pp. 3191-3195. In whole animal experiments, FK506 has been shown to stimulate nerve regeneration following facial nerve injury and results in functional recovery in animals with sciatic nerve lesions.

Several neurotrophic factors effecting specific neuronal populations in the central nervous system have been identified. For example, it has been hypothesized that Alzheimer's disease results from a decrease or loss of nerve growth factor (NGF). It has thus been proposed

to treat Alzheimer's patients with exogenous nerve growth factor or other neurotrophic proteins such as brain derived nerve factor (BDNF), glial derived nerve factor, ciliary neurotrophic factor, and neurotropin-3 to increase the survival of degenerating neuronal populations.

Clinical application of these proteins in various neurological disease states is hampered by difficulties in the delivery and bioavailability of large proteins to nervous system targets. By contrast, immunosuppressant drugs with neurotrophic activity are relatively small and display excellent bioavailability and specificity.

However, when administered chronically, immunosuppressants exhibit a number of potentially serious side effects including nephrotoxicity, such as impairment of glomerular filtration and irreversible interstitial fibrosis (Kopp et al., 1991, J. Am. Soc. Nephrol. 1:162); neurological deficits, such as involuntary tremors, or non-specific cerebral angina such as non-localized headaches (De Groen et al., 1987, N. Engl. J. Med. 317:861); and vascular hypertension with complications resulting therefrom (Kahan et al., 1989 N. Engl. J. Med. 321: 1725).

Accordingly, there is a need for small-molecule compounds which are useful for neurotrophic effects and for treating neurodegenerative disorders.

Hair loss occurs in a variety of situations. These situations include male pattern alopecia, alopecia senilis, alopecia areata, diseases accompanied by basic skin lesions or tumors, and systematic disorders such as nutritional disorders and internal secretion disorders. The mechanisms causing hair loss are very complicated, but in some instances can be attributed to aging, genetic disposition, the activation of male hormones, the loss of blood supply to hair follicles, and scalp abnormalities.

The immunosuppressant drugs FK506, rapamycin and cyclosporin are well known as potent T-cell specific immunosuppressants, and are effective against graft rejection after organ transplantation. It has been  
5 reported that topical, but not oral, application of FK506 (Yamamoto et al., J. Invest. Dermatol., 1994, 102, 160-164; Jiang et al., J. Invest. Dermatol. 1995, 104, 523-525) and cyclosporin (Iwabuchi et al., J. Dermatol. Sci. 1995, 9, 64-69) stimulates hair growth in a dose-dependent manner. One form of hair loss, alopecia areata, is known to be associated with autoimmune activities; hence, topically administered  
10 immunomodulatory compounds are expected to demonstrate efficacy for treating that type of hair loss. The hair growth stimulating effects of FK506 have been the subject of an international patent filing covering FK506 and structures related thereto for hair growth stimulation (Honbo et al., EP 0 423 714 A2). Honbo et al. discloses the use of relatively large tricyclic compounds, known for their immunosuppressive effects, as hair revitalizing agents.  
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The hair growth and revitalization effects of FK506 and related agents are disclosed in many U.S. patents (Goulet et al., U.S. Patent No. 5,258,389; Luly et al., U.S. Patent No. 5,457,111; Goulet et al., U.S. Patent No. 5,532,248; Goulet et al., U.S. Patent No. 5,189,042; and Ok et al., U.S. Patent No. 5,208,241; Rupprecht et al., U.S. Patent No. 5,284,840; Organ et al., U.S. Patent No. 5,284,877). These patents claim FK506 related compounds.  
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30 Although they do not claim methods of hair revitalization, they disclose the known use of FK506 for effecting hair growth. Similar to FK506 (and the claimed variations in the Honbo et al. patent), the compounds claimed in these patents are relatively large. Further,  
35 the cited patents relate to immunomodulatory compounds

for use in autoimmune related diseases, for which FK506's efficacy is well known.

Other U.S. patents disclose the use of cyclosporin and related compounds for hair revitalization (Hauer et al., U.S. Patent No. 5,342,625; Eberle, U.S. Patent No. 5,284,826; Hewitt et al., U.S. Patent No. 4,996,193). These patents also relate to compounds useful for treating autoimmune diseases and cite the known use of cyclosporin and related immunosuppressive compounds for hair growth.

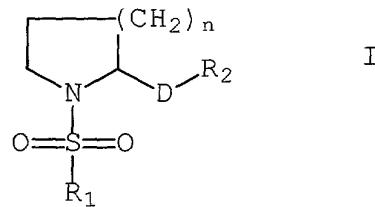
However, immunosuppressive compounds by definition suppress the immune system and also exhibit other toxic side effects. Accordingly, there is a need for small molecule compounds which are useful as hair revitalizing compounds.

#### SUMMARY OF THE INVENTION

The present invention relates to the surprising discovery that N-heterocyclic sulfonamide compounds containing a carboxylic acid or carboxylic acid isostere moiety may be useful for treating neurodegenerative disorders and for treating alopecia and promoting hair growth. Accordingly, a novel class of sulfonamide derivatives containing an acidic moiety or an isostere thereof attached to the 2-carbon of the N-heterocyclic ring are provided. These compounds stimulate neuronal regeneration and outgrowth and as such are useful for treating neurological disorders and neurodegenerative diseases. These compounds also promote hair growth and as such are useful for treating hair loss disorders. A preferred feature of the compounds of the present invention is that they do not exert any significant immunosuppressive activity and/or are non-immunosuppressive.

A preferred embodiment of this invention is a

compound having the formula (I):



where

5 n is 1-3;

R<sub>1</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>9</sub>, straight or branched chain alkyl, C<sub>2</sub>-C<sub>9</sub>, straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, or heterocycle;

D is a bond, or a C<sub>1</sub>-C<sub>10</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>10</sub> alkynyl;

R<sub>2</sub> is a carboxylic acid or a carboxylic acid isostere; wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or carboxylic acid isostere is optionally substituted with one or more substituents selected from R<sup>3</sup>, where

R<sup>3</sup> is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, alkylthio, sulfonyl, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO<sub>2</sub>R<sup>4</sup> where R<sup>4</sup> is hydrogen or C<sub>1</sub>-C<sub>9</sub>, straight or branched chain alkyl or alkenyl;

20 or a pharmaceutically acceptable salt, ester or solvate thereof;

provided that:

when D is a bond, and R<sub>2</sub> is COOH,

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then  $R_1$  cannot be substituted naphthyl;  
further provided that:  
when D is a bond, and n is 1, and  $R_2$  is COOH or CONHR<sub>3</sub>,  
then  $R_1$  is not hydroxyl, methyl, ethyl, substituted or  
unsubstituted thioethyl, benzothiazole, substituted  
benzopyran, substituted benzopyrrole, substituted  
benzoxazole, substituted 5-membered heterocycle  
containing two N and one S heteroatoms, or substituted or  
unsubstituted phenyl, phenylethyl, naphthyl, pyridyl,  
thienyl, quinoline, tricyclic ring, aminoethyl, or  
benzyl;

further provided that:  
when D is a bond, and n is 2, and  $R_2$  is COOH or  
phenylbutyl ester,  
then  $R_1$  is not substituted phenyl, or a substituted  
bicyclic ring containing two oxygen heteroatoms.

further provided that:  
when D is a bond, and n is 1-2, and  $R_2$  is a substituted or  
unsubstituted carbocyclic or heterocyclic ring structure,  
then  $R_1$  is not substituted or unsubstituted carbocycle or  
heterocycle, or hydroxy;

further provided that:  
when D is a bond, and n is 1-2, and  $R_2$  is hydroxy, alkoxy,  
 $-SO_2$ (phenyl),  $N(R_3)_2$ , substituted thio or alkylthio,  $-NCO$ ,  
 $-PO_3(Me)_2$ , or  $-NCOOC(ethyl)phenyl$ ,  
then  $R_1$  is not naphthalene, ethylene, substituted  
tricyclic ring, or substituted or unsubstituted phenyl;

further provided that:  
when D is C<sub>1</sub>-C<sub>3</sub> alkyl or hexenyl, and  $R_2$  is hydroxyl,  
then  $R_1$  is not substituted or unsubstituted phenyl, or  
benzoimidazole;

further provided that:  
when D is methyl, and n is 1, and  $R_2$  is cyano or COOH,  
then  $R_1$  is not substituted phenyl;

further provided that:

when D is methyl, and n is 1, and R<sub>2</sub> is methoxy or N(R<sub>3</sub>)<sub>2</sub>, then R<sub>1</sub> is not methyl, ethyl, phenylethyl, chloro substituted alkyl, substituted oxirane, substituted aziridine wherein one of the carbons is replaced with an oxygen, substituted or unsubstituted propenyl, substituted phenyl, benzyl, or trifluoro substituted C<sub>2</sub>-C<sub>3</sub> alkyl or alkenyl;

further provided that:

when D is ethyl, and n is 2, and R<sub>2</sub> is hydroxyl or N(R<sub>3</sub>)<sub>2</sub>, then R<sub>1</sub> is not naphthyl;

further provided that:

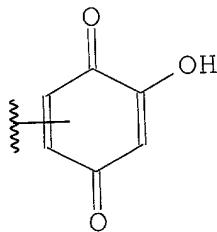
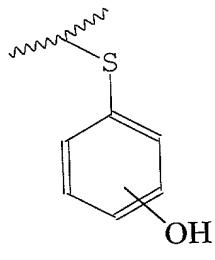
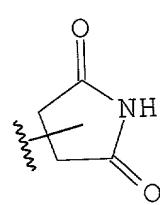
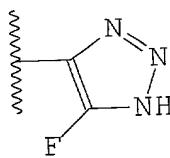
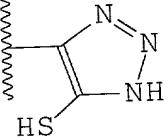
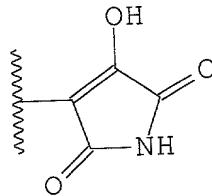
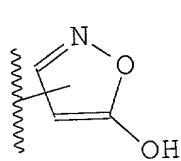
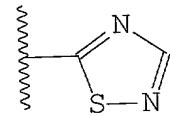
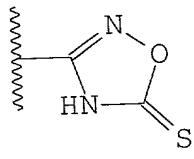
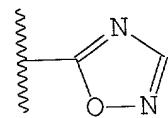
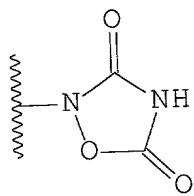
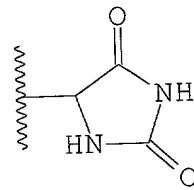
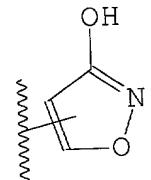
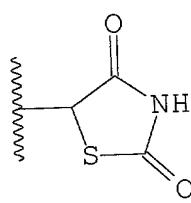
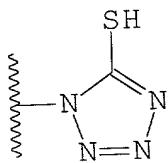
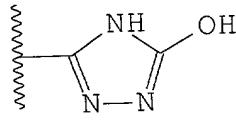
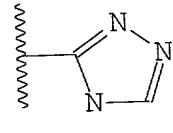
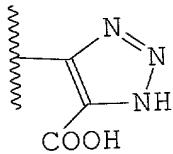
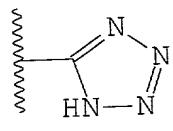
when D is propyl, and n is 1, and R<sub>2</sub> is methoxy, then R<sub>1</sub> is not ethylene, cyano substituted ethyl, or triethoxy substituted propyl;

further provided that:

when D is not a bond and at least one of D and R<sub>2</sub> contains at least one S or O, then R<sub>1</sub> is not methyl or substituted phenyl.

A preferred embodiment of this invention is where R<sub>2</sub> is a carbocycle or heterocycle containing any combination of CH<sub>2</sub>, O, S, or N in any chemically stable oxidation state, where any of the atoms of said ring structure are optionally substituted in one or more positions with R<sup>3</sup>.

Especially preferred embodiments of this invention are where R<sub>2</sub> is selected from the group below:



where the atoms of said ring structure may be optionally substituted at one or more positions with R<sup>3</sup>.

Another preferred embodiment of this invention is where R<sub>2</sub> is selected from the group consisting of -COOH, -SO<sub>3</sub>H, -SO<sub>2</sub>HNR<sup>3</sup>, -PO<sub>2</sub>(R<sup>3</sup>)<sub>2</sub>, -CN, -PO<sub>3</sub>(R<sup>3</sup>)<sub>2</sub>, -OR<sup>3</sup>, -SR<sup>3</sup>, -NHCOR<sup>3</sup>, -N(R<sup>3</sup>)<sub>2</sub>, -CON(R<sup>3</sup>)<sub>2</sub>, -CONH(O)R<sup>3</sup>, -CONHNHSO<sub>2</sub>R<sup>3</sup>, -COHNSO<sub>2</sub>R<sup>3</sup>, and -CONR<sup>3</sup>CN.

Preferred embodiments of this invention are compounds of the formula: (2S)-1-(phenylmethyl)sulfonyl-2-hydroxymethyl pyrrolidine; (2S)-1-(phenylmethyl)sulfonyl-2-pyrrolidinetetrazole; (2S)-1-(phenylmethyl) sulfonyl-2-pyrrolidine carbonitrile; and compounds 1-136.

Another preferred embodiment of this invention is a composition containing: a therapeutically effective amount of a compound of formula (I); a neurotrophic factor different from formula (I); and a pharmaceutically suitable carrier.

Another preferred embodiment of the invention is a method of promoting neuronal regeneration and growth in mammals, comprising administering to a mammal an effective amount of a N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere.

Another preferred embodiment of the invention is a method of treating a neurological disorder in an animal, comprising administering to an animal a therapeutically effective amount of a N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere to stimulate growth of damaged peripheral nerves or to promote neuronal regeneration.

Yet another preferred embodiment of the invention is a method of preventing neurodegeneration in an animal, comprising administering to an animal an effective amount of an N-linked sulfonamide of an N-heterocyclic

carboxylic acid or carboxylic acid isostere.

Yet another preferred embodiment of the invention is a method of treating alopecia or promoting hair growth in an animal, comprising administering to an animal an effective amount of an N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a photograph of C57 Black 6 mice before being shaved for the hair regeneration experiment.

Figure 2 is a photograph of mice treated with a vehicle after six weeks. Figure 2 shows that less than 3% of the shaved area is covered with new hair growth when the vehicle (control) is administered.

Figure 3 is a bar graph illustrating relative hair growth on shaved mice treated with N-heterocyclic carboxylic acids or carboxylic acid isosteres at 1 $\mu$ mole per milliliter three times per week. Hair growth was evaluated after 14 days of treatment.

#### DETAILED DESCRIPTION OF THE INVENTION

##### Definitions

"Alkyl" means a branched or unbranched saturated hydrocarbon chain comprising a designated number of carbon atoms. For example, C<sub>1</sub>-C<sub>6</sub> straight or branched alkyl hydrocarbon chain contains 1 to 6 carbon atoms, and includes but is not limited to substituents such as methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, tert-butyl, n-pentyl, n-hexyl, and the like. It is also contemplated as within the scope of the present invention that "alkyl" may also refer to a hydrocarbon chain wherein any of the carbon atoms of said alkyl are optionally replaced with O, NH, S, or SO<sub>2</sub>. For example, carbon 2 of n-pentyl can be replaced with O to form propyloxymethyl.

"Alkenyl" means a branched or unbranched unsaturated hydrocarbon chain comprising a designated number of carbon atoms. For example, C<sub>2</sub>-C<sub>6</sub> straight or branched alkenyl hydrocarbon chain contains 2 to 6 carbon atoms having at least one double bond, and includes but is not limited to substituents such as ethenyl, propenyl, iso-propenyl, butenyl, iso-butenyl, tert-butenyl, n-pentenyl, n-hexenyl, and the like. It is also contemplated as within the scope of the present invention that "alkenyl" may also refer to an unsaturated hydrocarbon chain wherein any of the carbon atoms of said alkenyl are optionally replaced with O, NH, S, or SO<sub>2</sub>. For example, carbon 2 of 4-pentene can be replaced with O to form (2-propene)oxymethyl.

"Alkoxy" means the group -OR wherein R is alkyl as herein defined. Preferably, R is a branched or unbranched saturated hydrocarbon chain containing 1 to 6 carbon atoms.

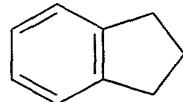
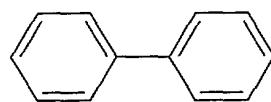
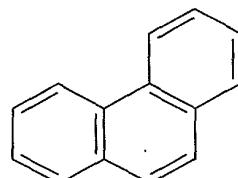
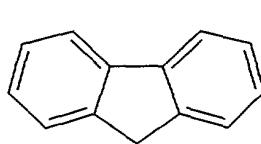
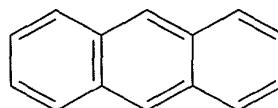
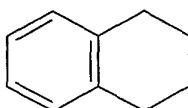
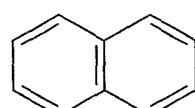
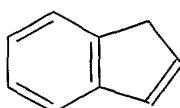
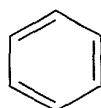
The term "carbocycle" or refers to an organic cyclic moiety in which the cyclic skeleton is comprised of only carbon atoms whereas the term "heterocycle" refers to an organic cyclic moiety in which the cyclic skeleton contains one or more heteroatoms selected from nitrogen, oxygen, or sulfur and which may or may not include carbon atoms.

Thus, the term "carbocycle" refers to a carbocyclic moiety containing the indicated number of carbon atoms. The term "C<sub>3</sub>-C<sub>8</sub> cycloalkyl", therefore, refers to an organic cyclic substituent in which three to eight carbon atoms form a three, four, five, six, seven, or eight-membered ring, including, for example, a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl ring. As used herein, "carbocycle" may also refer to two or more cyclic ring systems which are fused to form, for example bicyclic, tricyclic, or other

similar bridged substituents (e.g. adamantyl).

"Aryl" refers to an aromatic carbocyclic group having a single ring, for example a phenyl ring; multiple rings, for example biphenyl; or multiple condensed rings in which at least one ring is aromatic, for example naphthyl, 1,2,3,4-tetrahydronaphthyl, anthryl, or phenanthryl, which can be unsubstituted or substituted with one or more other substituents as defined above. The substituents attached to a phenyl ring portion of an aryl moiety in the compounds of Formula (I) may be configured in the ortho-, meta-, or para- orientations.

Examples of typical aryl moieties included in the scope of the present invention may include, but are not limited to, the following:



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"Aralkyl" refers to alkyl or alkylene (alkenyl) chain which is substituted with aryl, heteroaryl, carbocycle or heterocycle, or alternatively one or more aryl, heteroaryl, carbocycle, or heterocycle(s) which is/are substituted with alkyl or alkenyl, i.e.

'Alkyl/alkylene which is substituted with Ar' or 'Ar which is substituted with alkyl/alkylene'

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"Heterocycle" refers to a saturated, unsaturated, or aromatic carbocyclic group having a single ring, multiple rings, or multiple condensed rings, and having at least one hetero atom such as nitrogen, oxygen, or sulfur within at least one of the rings. "Heteroaryl" refers to a heterocycle in which at least one ring is aromatic.

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Any of the heterocyclic or heteroaryl groups can be unsubstituted or optionally substituted with one or more groups as defined above. Further, bi- or tri-cyclic heteroaryl moieties may comprise at least one ring which is either completely or partially saturated.

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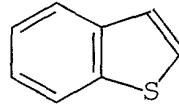
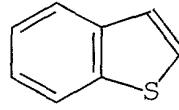
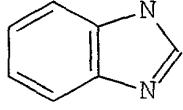
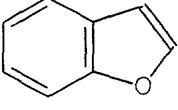
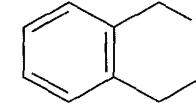
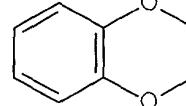
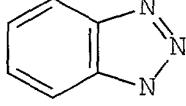
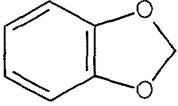
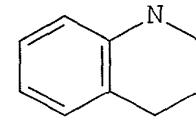
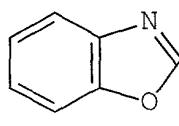
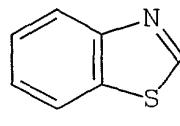
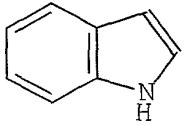
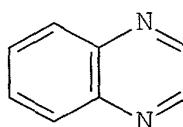
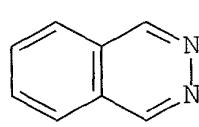
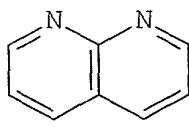
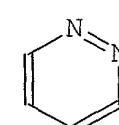
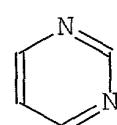
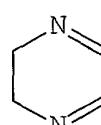
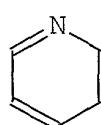
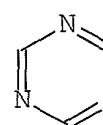
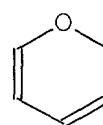
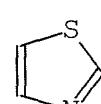
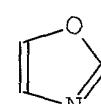
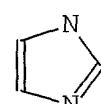
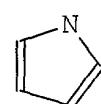
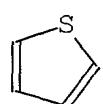
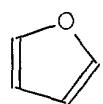
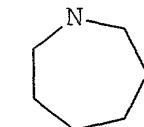
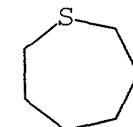
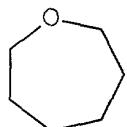
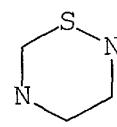
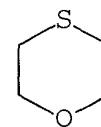
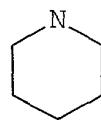
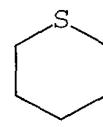
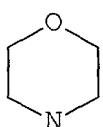
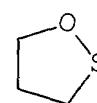
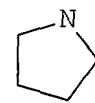
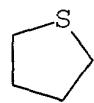
As one skilled in the art will appreciate, such heterocyclic moieties may exist in several isomeric forms, all of which are encompassed by the present invention. For example, a 1,3,5-triazine moiety is isomeric to a 1,2,4-triazine group. Such positional isomers are to be considered within the scope of the present invention. Likewise, the heterocyclic or heteroaryl groups can be bonded to other moieties in the compounds of the present invention. The point(s) of attachment to these other moieties is not to be construed as limiting on the scope of the invention. Thus, by way of example, a pyridyl moiety may be bound to other groups through the 2-, 3-, or 4-position of the pyridyl group. All such configurations are to be construed as within the scope of the present invention.

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Examples of heterocyclic or heteroaryl moieties included in the scope of the present invention may

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include, but are not limited to, the following:



"Halo" means at least one fluoro, chloro, bromo, or iodo moiety.

The term "pharmaceutically acceptable salt, ester, or solvate" refers to salt, ester, or solvates of the subject compounds which possess the desired pharmacological activity and which are neither biologically nor otherwise undesirable. The salt, ester, or solvates can be formed with inorganic or organic acids such as acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, gluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, naphthylate, 2-naphthalenesulfonate, nicotinate, oxalate, sulfate, thiocyanate, tosylate and undecanoate. Base salt, ester, or solvates include ammonium salts, alkali metal salts such as lithium, sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salt with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quaternized with such agents as: 1) lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; 2) dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; 3) long chain alkyls such as decyl, lauryl, myristyl and stearyl substituted with one or more halide such as chloride, bromide and iodide; and 4) aryl or arylalkyl halides like benzyl and phenethyl bromide and others.

The compounds of this invention may possess at least one asymmetric center and thus can be produced as

mixtures of stereoisomers or as individual enantiomers or diastereomers. The individual stereoisomers may be obtained by using an optically active starting material, by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis, or by resolution of the compound of formula (I). It is understood that the individual stereoisomers as well as mixtures (racemic and non-racemic) of stereoisomers are encompassed by the scope of the present invention. The S-stereoisomer at atom 1 of formula I is a most preferred embodiment of the invention.

"Stereoisomers" are isomers that differ only in the way the atoms are arranged in space.

"Isomers" are different compounds that have the same molecular formula and includes cyclic isomers such as (iso)indole and other isomeric forms of cyclic moieties.

"Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other.

"Diastereoisomers" are stereoisomers which are not mirror images of each other.

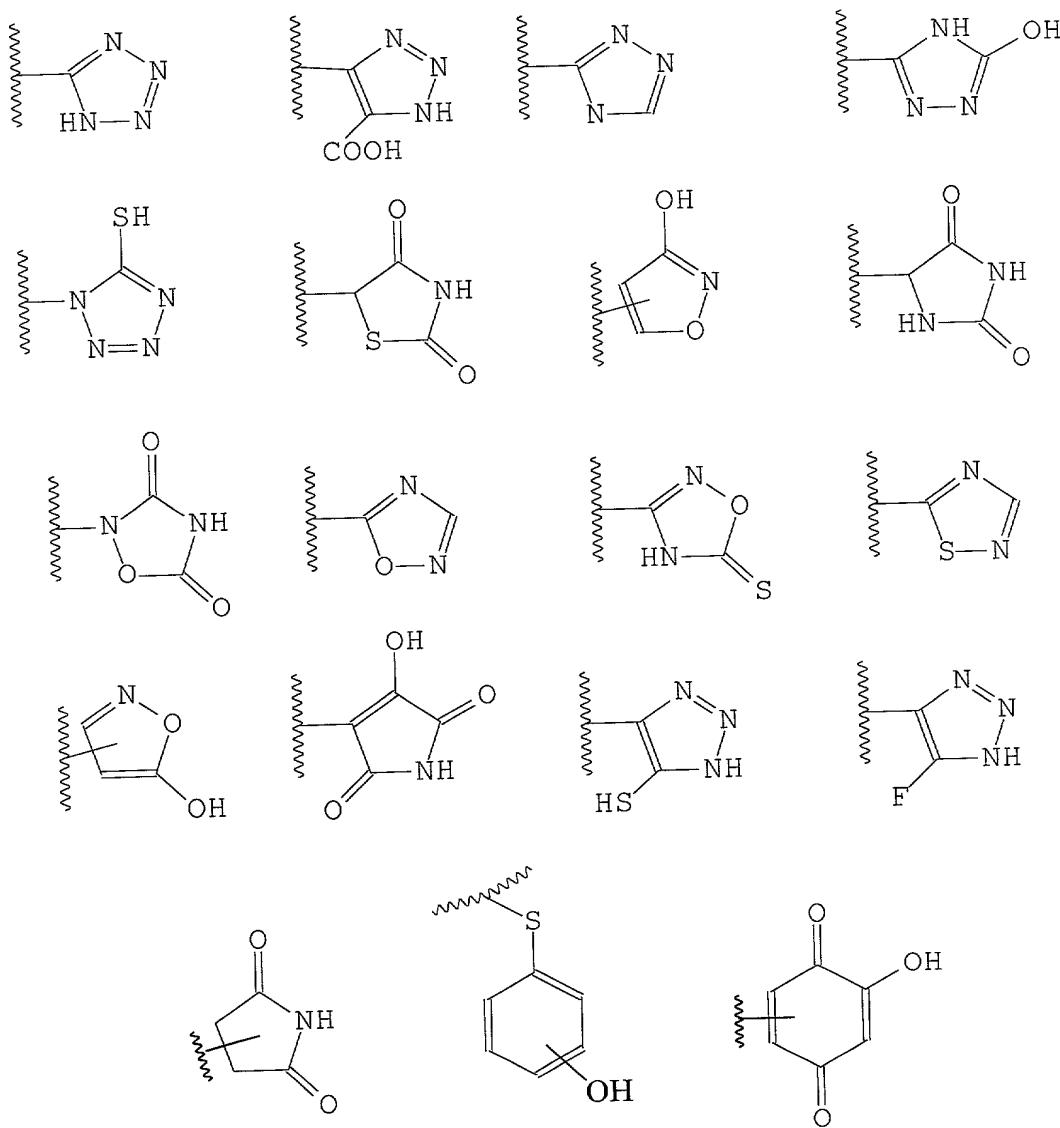
"Racemic mixture" means a mixture containing equal parts of individual enantiomers. "Non-racemic mixture" is a mixture containing unequal parts of individual enantiomers or stereoisomers.

"Isosteres" are different compounds that have different molecular formulae but exhibit the same or similar properties. For example, tetrazole is an isostere of carboxylic acid because it mimics the properties of carboxylic acid even though they both have very different molecular formulae. Tetrazole is one of many possible isosteric replacements for carboxylic acid. Other carboxylic acid isosteres contemplated by the present invention include

-COOH, -SO<sub>3</sub>H, -SO<sub>2</sub>HN<sup>R</sup><sup>3</sup>, -PO<sub>2</sub>(R<sup>3</sup>)<sub>2</sub>, -CN, -PO<sub>3</sub>(R<sup>3</sup>)<sub>2</sub>, -OR<sup>3</sup>, -SR<sup>3</sup>, -NHCOR<sup>3</sup>, -N(R<sup>3</sup>)<sub>2</sub>, -CON(R<sup>3</sup>)<sub>2</sub>, -CONH(O)R<sup>3</sup>, -CONHNHSO<sub>2</sub>R<sup>3</sup>,

$-\text{COHNSO}_2\text{R}^3$ , and  $-\text{CONR}^3\text{CN}$ .

In addition, carboxylic acid isosteres can include 5-7 membered carbocycles or heterocycles containing any combination of  $\text{CH}_2$ , O, S, or N in any chemically stable oxidation state, where any of the atoms of said ring structure are optionally substituted in one or more positions. The following structures are non-limiting examples of preferred carbocyclic and heterocyclic isosteres contemplated by this invention.



where the atoms of said ring structure may be optionally substituted at one or more positions with R<sup>3</sup>. The present invention contemplates that when chemical substituents are added to a carboxylic isostere then the inventive compound retains the properties of a carboxylic isostere. The present invention contemplates that when a carboxylic isostere is optionally substituted with one or more moieties selected from R<sup>3</sup>, then the substitution can not eliminate the carboxylic acid isosteric properties of the inventive compound. The present invention contemplates that the placement of one or more R<sup>3</sup> substituents upon a carbocyclic or heterocyclic carboxylic acid isostere shall not be at an atom(s) which maintains or is integral to the carboxylic acid isosteric properties of the inventive compound if such a substituent(s) would destroy the carboxylic acid isosteric properties of the inventive compound.

Other carboxylic acid isosteres not specifically exemplified or described in this specification are also contemplated by the present invention.

The term "preventing neurodegeneration" as used herein includes the ability to inhibit or prevent neurodegeneration in patients newly diagnosed as having a neurodegenerative disease, or at risk of developing a new degenerative disease and for inhibiting or preventing further neurodegeneration in patients who are already suffering from or have symptoms of a neurodegenerative disease when the compounds are given concurrently.

The term "treatment" as used herein covers any treatment of a disease and/or condition in an animal, particularly a human, and includes:

(i) preventing a disease and/or condition from occurring in a subject which may be predisposed to the disease and/or condition but has not yet been diagnosed as having it;

(ii) inhibiting the disease and/or condition, i.e., arresting its development; or

(iii) relieving the disease and/or condition, i.e., causing regression of the disease and/or condition.

5 The system used in naming the compounds of the present invention is shown below, using a compound of formula I as an example.

10 A compound of the present invention, especially formula I, wherein n is 1, D is a bond, R<sub>1</sub> is phenylmethyl, and R<sub>2</sub> is -CN, is named (2S)-1-(phenylmethyl) sulfonyl-2-pyrrolidine carbonitrile.

15 "Alopecia" refers to deficient hair growth and partial or complete loss of hair, including without limitation androgenic alopecia (male pattern baldness), toxic alopecia, alopecia senilis, alopecia areata, alopecia pelada and trichotillomania. Alopecia results when the pilar cycle is disturbed. The most frequent phenomenon is a shortening of the hair growth or anagen phase due to cessation of cell proliferation. This results in an early onset of the catagen phase, and consequently a large number of hairs in the telogen phase during which the follicles are detached from the dermal papillae, and the hairs fall out. Alopecia has a number of etiologies, including genetic factors, aging, local and systemic diseases, febrile conditions, mental stresses, hormonal problems, and secondary effects of drugs.

20 "Pilar cycle" refers to the life cycle of hair follicles, and includes three phases:

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- 30 (1) the anagen phase, the period of active hair growth which, insofar as scalp hair is concerned, lasts about three to five years;
- 35 (2) the catagen phase, the period when growth stops and the follicle atrophies which, insofar as scalp hair is concerned, lasts about one to two

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weeks; and

(3) the telogen phase, the rest period when hair progressively separates and finally falls out which, insofar as scalp hair is concerned, lasts about three to four months.

Normally 80 to 90 percent of the follicles are in the anagen phase, less than 1 percent being in the catagen phase, and the rest being in the telogen phase. In the telogen phase, hair is uniform in diameter with a slightly bulbous, non-pigmented root. By contrast, in the anagen phase, hair has a large colored bulb at its root.

"Promoting hair growth" refers to maintaining, inducing, stimulating, accelerating, or revitalizing the germination of hair.

"Treating alopecia" refers to:

(i) preventing alopecia in an animal which may be predisposed to alopecia; and/or

(ii) inhibiting, retarding or reducing alopecia; and/or

(iii) promoting hair growth; and/or

(iv) prolonging the anagen phase of the hair cycle; and/or

(v) converting vellus hair to growth as terminal hair. Terminal hair is coarse, pigmented, long hair in which the bulb of the hair follicle is seated deep in the dermis. Vellus hair, on the other hand, is fine, thin, non-pigmented short hair in which the hair bulb is located superficially in the dermis. As alopecia progresses, the hairs change from the terminal to the vellus type.

The term "neurotrophic" as used herein includes without limitation the ability to stimulate neuronal regeneration or growth and/or the ability to prevent or treat neurodegeneration.

The term "non-immunosuppressive" refers to the inability of the compounds of the present invention to trigger an immune response when compared to a control such as FK506 or cyclosporin A. Assays for determining immunosuppression are well known to those of ordinary skill in the art. Specific non-limiting examples of well known assays include PMA and OKT3 assays wherein mitogens are used to stimulate proliferation of human peripheral blood lymphocytes (PBL). Compounds added to such assay systems are evaluated for their ability to inhibit such proliferation.

#### Compounds of the Invention

The present invention relates to the surprising discovery that N-linked sulfonamides of N-heterocyclic carboxylic acid or carboxylic acid isostere compounds are neurotrophic and are able to treat alopecia. Accordingly, a novel class of compounds are provided. A preferred feature of the compounds of the present invention is that they do not exert any significant immunosuppressive activity.

Preferred compounds of the present invention contain carboxylic acid moieties and other isosteric replacements for carboxylic acid moieties, of which several examples are specified herein. Other isosteric replacements for carboxylic acid moieties, known to those skilled in the art of medicinal chemistry, are within the scope of the invention if not otherwise specified.

The neurotrophic compounds of this invention can be periodically administered to a patient undergoing treatment for neurological disorders or for other reasons in which it is desirable to stimulate neuronal regeneration and growth, such as in various peripheral neuropathic and neurological disorders relating to neurodegeneration. The compounds of this invention can also be administered to mammals other than humans for

treatment of various mammalian neurological disorders.

The novel compounds of the present invention possess an excellent degree of neurotrophic activity. This activity is useful in the stimulation of damaged neurons, the promotion of neuronal regeneration, the prevention of neurodegeneration, and in the treatment of several neurological disorders known to be associated with neuronal degeneration and peripheral neuropathies. The neurological disorders that may be treated include but are not limited to: trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, amyotrophic lateral sclerosis, progressive muscular atrophy, progressive bulbar inherited muscular atrophy, herniated, ruptured or prolapsed invertebrate disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathic such as those caused by lead, dapson, ticks, prophyria, or Gullain-Barré syndrome, Alzheimer's disease, and Parkinson's disease.

The above discussion relating to the utility and administration of the compounds of the present invention also applies to the pharmaceutical compositions of the present invention.

The term "pharmaceutically acceptable carrier" as used herein refers to any carrier, diluent, excipient, suspending agent, lubricating agent, adjuvant, vehicle, delivery system, emulsifier, disintegrant, absorbant, preservative, surfactant, colorant, flavorant, or sweetener.

For these purposes the compounds of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir in dosage formulations containing conventional non-toxic

pharmaceutically-acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intraperitoneally, intrathecally, intraventricularly, 5 intrasternal and intracranial injection or infusion techniques.

For oral administration, the compounds of the present invention may be provided in any suitable dosage form known in the art. For example, the compositions may be incorporated into tablets, powders, granules, beads, 10 chewable lozenges, capsules, liquids, aqueous suspensions or solutions, or similar dosage forms, using conventional equipment and techniques known in the art. Tablet dosage forms are preferred. Tablets may contain carriers such as lactose and corn starch, and/or lubricating agents such as magnesium stearate. Capsules may contain diluents including lactose and dried corn starch. Aqueous suspensions may contain emulsifying and suspending agents combined with the active ingredient.

When preparing dosage form incorporating the compositions of the invention, the compounds may also be blended with conventional excipients such as binders, including gelatin, pregelatinized starch, and the like; lubricants, such as hydrogenated vegetable oil, stearic acid, and the like; diluents, such as lactose, mannose, 25 and sucrose; disintegrants, such as carboxymethylcellulose and sodium starch glycolate; suspending agents, such as povidone, polyvinyl alcohol, and the like; absorbants, such as silicon dioxide; preservatives, such as methylparaben, propylparaben, and sodium benzoate; surfactants, such as sodium lauryl sulfate, polysorbate 80, and the like; colorants such as F.D. & C. dyes and lakes; flavorants; and sweeteners.

Compositions and methods of the invention also may 30 utilize controlled release technology. Thus, for

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example, the inventive compounds may be incorporated into a hydrophobic polymer matrix for controlled release over a period of days. Such controlled release films are well known to the art. Particularly preferred are transdermal delivery systems. Other examples of polymers commonly employed for this purpose that may be used in the present invention include nondegradable ethylene-vinyl acetate copolymer and degradable lactic acid-glycolic acid copolymers which may be used externally or internally. Certain hydrogels such as poly(hydroxyethylmethacrylate) or poly(vinylalcohol) also may be useful, but for shorter release cycles than the other polymer releases systems, such as those mentioned above.

To be effective therapeutically as central nervous system targets, the compounds of the present invention should readily penetrate the blood-brain barrier when peripherally administered. Compounds which cannot penetrate the blood-brain barrier can be effectively administered by an intraventricular route or other appropriate delivery system suitable for administration to the brain.

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The compounds of the present invention may be administered in the form of sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparations may also be sterile injectable solutions or suspensions in non-toxic parenterally-acceptable diluents or solvents, for example, as solutions in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as solvents or suspending

mediums. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids such as oleic acid and its glyceride derivatives, including olive oil and castor oil, especially in their polyoxyethylated versions, are useful in the preparation of injectables. These oil solutions or suspensions may also contain long-chain alcohol diluents or dispersants.

The compounds of this invention may also be administered rectally in the form of suppositories. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at room temperature, but liquid at rectal temperature and, therefore, will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The compounds of this invention may also be administered topically, especially when the conditions addressed for treatment involve areas or organs readily accessible by topical application, including neurological disorders of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas.

For topical application to the eye, or ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively for the ophthalmic uses the compounds may be formulated in an ointment such as petrolatum.

For topical application to the skin, the compounds can be formulated in a suitable ointment containing the compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil,

liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the compounds can be formulated in a suitable lotion or cream containing the active compound suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation.

Dosage levels on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 0.1 mg to about 1,000 mg. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Typically, *in vitro* dosage-effect results provide useful guidance on the proper doses for patient administration. Studies in animal models are also helpful. The considerations for determining the proper dose levels are well known in the art.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the severity of the particular disease being treated and form of administration.

To effectively treat alopecia or promote hair growth, the compounds used in the inventive methods and pharmaceutical compositions must readily affect the targeted areas. For these purposes, the compounds are

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preferably administered topically to the skin.

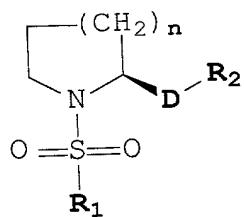
For topical application to the skin, the compounds can be formulated into suitable ointments containing the compounds suspended or dissolved in, for example, mixtures with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the compounds can be formulated into suitable lotions or creams containing the active compound suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 60, cetyl ester wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds can be administered for treatment of hair loss with other hair revitalizing agents. Specific dose levels for the other hair revitalizing agents will depend upon the factors previously stated and the effectiveness of the drug combination.

Other routes of administration known in the pharmaceutical art are also contemplated by this invention.

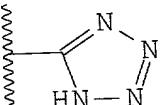
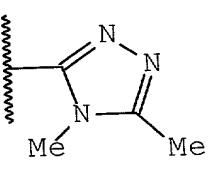
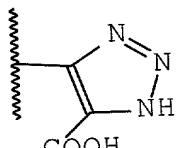
Specific embodiments of the inventive compounds are presented in Table I. The present invention contemplates employing the compounds of Table I, below, for use in compositions and methods to prevent and/or treat a neurological disorder in an animal, and for use in compositions and methods to treat alopecia and promote hair growth in an animal, and all other uses suggested in this specification.

TABLE I

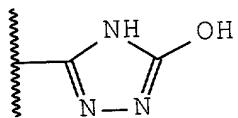


	No.	n	D	R2	R1
5	1	1	bond	COOH	Benzyl
	2	1	bond	COOH	$\alpha$ -MethylBenzyl
	3	1	bond	COOH	4-MethylBenzyl
	4	1	bond	Tetrazole	Benzyl
	5	1	bond	SO <sub>3</sub> H	$\alpha$ -MethylBenzyl
	6	1	CH <sub>2</sub>	COOH	4-MethylBenzyl
	7	1	bond	SO <sub>2</sub> HNMe	Benzyl
	8	1	bond	CN	$\alpha$ -MethylBenzyl
	No.	n	D	R2	R1
10	9	1	bond	PO <sub>3</sub> H <sub>2</sub>	4-MethylBenzyl
	10	2	bond	COOH	Benzyl
	11	2	bond	COOH	$\alpha$ -MethylBenzyl
	12	2	bond	COOH	4-MethylBenzyl
	13	2	bond	COOH	3,4,5-trimethoxy phenyl
15	14	2	bond	COOH	Cyclohexyl
	15	2	bond	PO <sub>2</sub> HET	i-propyl
	16	2	bond	PO <sub>3</sub> HPropyl	ethyl
	17	2	bond	PO <sub>3</sub> (Et) <sub>2</sub>	Methyl
	18	2	bond	OMe	tert-butyl
	19	2	bond	OEt	n-pentyl
	20	2	bond	OPropyl	n-hexyl
20	21	1	bond	OButyl	Cyclohexyl
	22	1	bond	OPentyl	cyclopentyl
	23	1	bond	OHexyl	n-heptyl

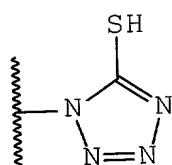
	24	1	bond	SMe	n-octyl
	25	1	bond	SEt	n-nonyl
	26	2	bond	SPropyl	2-indolyl
	27	2	bond	SButyl	2-furyl
5	28	2	bond	NHCOMe	2-thiazolyl
	29	2	bond	NHCOEt	2-thienyl
	30	1	CH <sub>2</sub>	N(Me) <sub>2</sub>	2-pyridyl
	31	1	(CH <sub>2</sub> ) <sub>2</sub>	N(Me)Et	benzyl
	32	1	(CH <sub>2</sub> ) <sub>3</sub>	CON(Me) <sub>2</sub>	benzyl
10	33	1	(CH <sub>2</sub> ) <sub>4</sub>	CONHMe	benzyl
	34	1	(CH <sub>2</sub> ) <sub>5</sub>	CONHET	benzyl
	35	1	(CH <sub>2</sub> ) <sub>6</sub>	CONHPropyl	1,1-dimethylpropyl
	36	1	bond	CONH(O)Me	Benzyl
15	37	1	bond	CONH(O)Et	$\alpha$ -Methylphenyl
	38	1	bond	CONH(O)Propyl	4-Methylphenyl
	39	2	bond	COOH	Benzyl
	40	2	bond	COOH	$\alpha$ -Methylphenyl
	41	2	bond	COOH	4-Methylphenyl
	<b>No.</b>	<b>n</b>	<b>D</b>	<b>R2</b>	<b>R1</b>
20	42	1	CH <sub>2</sub>	COOH	benzyl
	43	1	(CH <sub>2</sub> ) <sub>2</sub>	COOH	benzyl
	44	1	(CH <sub>2</sub> ) <sub>3</sub>	COOH	benzyl
	45	1	(CH <sub>2</sub> ) <sub>4</sub>	COOH	benzyl
	46	1	(CH <sub>2</sub> ) <sub>5</sub>	COOH	benzyl
25	47	1	(CH <sub>2</sub> ) <sub>6</sub>	COOH	benzyl
	48	1	(CH <sub>2</sub> ) <sub>7</sub>	COOH	benzyl
	49	1	(CH <sub>2</sub> ) <sub>8</sub>	COOH	benzyl
	50	1	(CH <sub>2</sub> ) <sub>9</sub>	COOH	benzyl
	51	1	(CH <sub>2</sub> ) <sub>10</sub>	COOH	benzyl
30	52	1	C <sub>2</sub> H <sub>2</sub>	COOH	benzyl
	53	1	2-OH,Et	COOH	benzyl
	54	1	2butylene	COOH	benzyl
	55	1	i-Pro	COOH	benzyl
	56	1	tert-Bu	COOH	benzyl
35	57	1	2-nitro	COOH	benzyl

			Hexyl	
	58	3	(CH <sub>2</sub> ) <sub>2</sub>	CN
	59	1	(CH <sub>2</sub> ) <sub>3</sub>	CN
	60	3	bond	CONHNHSO <sub>2</sub> Me
5	61	3	bond	CONHNHSO <sub>2</sub> Et
	62	3	bond	CONHSO <sub>2</sub> Me
	63	2	bond	CONHNHSO <sub>2</sub> Et
	64	2	bond	CON(Me) CN
	65	2	bond	CON(Et) CN
10	66	1	(CH <sub>2</sub> ) <sub>2</sub>	COOH
	67	1	(CH <sub>2</sub> ) <sub>3</sub>	COOH
	68	1	(CH <sub>2</sub> ) <sub>4</sub>	COOH
	69	1	(CH <sub>2</sub> ) <sub>5</sub>	COOH
	70	1	(CH <sub>2</sub> ) <sub>6</sub>	COOH
	71	1	(CH <sub>2</sub> ) <sub>7</sub>	COOH
	72	1	(CH <sub>2</sub> ) <sub>8</sub>	COOH
	73	1	(CH <sub>2</sub> ) <sub>9</sub>	COOH
	74	1	(CH <sub>2</sub> ) <sub>10</sub>	COOH
	<b>No.</b>	<b>n</b>	<b>D</b>	<b>R2</b>
15	75	1	C <sub>2</sub> H <sub>2</sub>	COOH
	76	1	bond	
20	77	1	bond	
	78	1	bond	
				<b>R1</b>
				Cyclohexyl
				benzyl
				benzyl
				benzyl

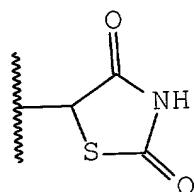
79 1 bond benzyl



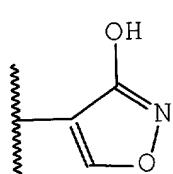
80 1 bond benzyl



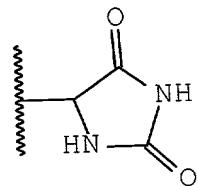
81 1 bond benzyl

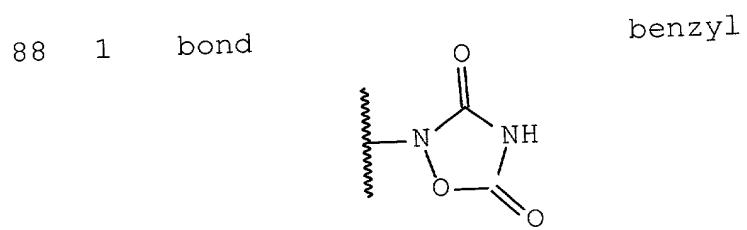
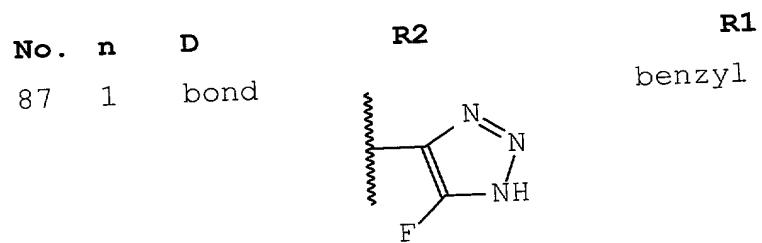
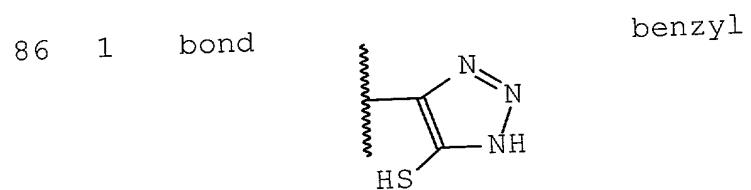
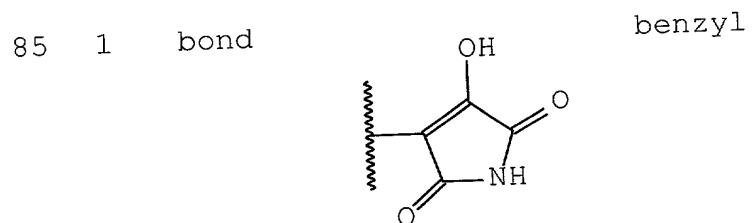
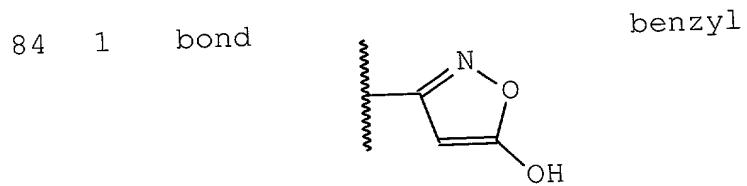


No. n D R2 R1  
82 1 bond benzyl



83 1 bond benzyl





89      1      bond      benzyl

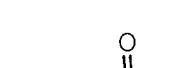
The diagram shows a vertical zigzag line representing a bond. At the top of the bond is a benzyl group (Et-CH=CH<sub>2</sub>). At the bottom of the bond is a nitrogen atom bonded to an oxygen atom, which is further bonded to another nitrogen atom. This second nitrogen atom is also bonded to a methyl group (CH<sub>3</sub>) and an ethyl group (Et).

90      1      bond      benzyl

The diagram shows a chemical structure. On the left, a vertical wavy line representing a bond extends downwards from the text 'bond'. At the bottom of this line is a benzyl group, which consists of a phenyl ring attached to a methylene group (-CH<sub>2</sub>-). This group is connected via a single bond to the nitrogen atom of a thiazolidine ring. The thiazolidine ring has a sulfur atom at the 4-position, double-bonded to an oxygen atom. The 5-position of the ring is double-bonded to a nitrogen atom, which is also double-bonded to another nitrogen atom above it.

91 1 bond  benzyl

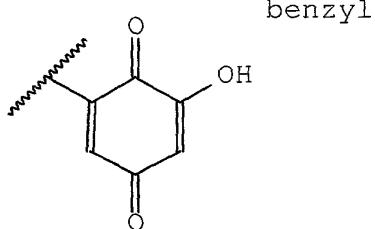
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No.	n	D	R2	R1
92	1	bond		benzyl

10      93      1      bond      benzyl

The diagram shows a benzene ring with a hydroxyl group (-OH) attached at the top position. At the adjacent position (position 1), there is a thiomethyl group (-S-CH<sub>2</sub>-). A wavy line connects the sulfur atom to the methyl group, indicating a single bond.

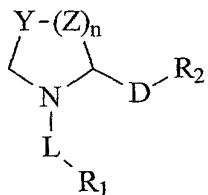
94 1 bond



95	1	bond	$\text{CH}_2\text{OH}$	benzyl
96	1	bond	$\text{CONH}_2$	benzyl
97	1	bond	CN	benzyl

Additional claimed or comparative carboxylic acids and isosteres of N-heterocyclic compounds which also show the remarkable neurotrophic and hair growth effects of the present invention are shown below in Table II:

TABLE II



Cpd	n	D	R <sub>2</sub>	L	R <sub>1</sub>
5	A	1	bond	COOH	SO <sub>2</sub> Benzyl
	B	1	bond	CONH <sub>2</sub>	SO <sub>2</sub> Benzyl
	C	1	bond	-CN	SO <sub>2</sub> Benzyl
	D	1	bond	tetrazole	SO <sub>2</sub> Benzyl
	E	1	CH <sub>2</sub>	-OH	SO <sub>2</sub> Benzyl
10	F	1	bond	COOH	1,2-dioxoethyl 1,1-dimethylpropyl
	G	2	bond	COOH	1,2-dioxoethyl 1,1-dimethylpropyl
	H	1	CH <sub>2</sub>	OH	1,2-dioxoethyl 1,1-dimethylpropyl
	I	1	bond	tetrazole	1,2-dioxoethyl 1,1-dimethylpropyl
	J	1	bond	-CN	1,2-dioxoethyl 1,1-dimethylpropyl
15	K	2	bond	CONH <sub>2</sub>	1,2-dioxoethyl 1,1-dimethylpropyl
					where Y and Z are both carbon for compounds A-K,
	L	1	bond	COOH	1,2-dioxoethyl 1,1-dimethylpropyl
	M	1	bond	COOH	1,2-dioxoethyl 1,1-dimethylpropyl
					where Z is S for compound H or
20					where Y is S for compound I.

Pharmaceutical Compositions of the Present Invention

The present invention relates to a pharmaceutical composition comprising:

25 (i) an effective amount of an N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere compound; and  
(ii) a pharmaceutically acceptable carrier.

The present invention also relates to a pharmaceutical composition comprising:

(i) an effective amount of an N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere compound for treating neurodegenerative diseases, neurological disorders, and nerve damage, or promoting nerve growth in an animal; and

(ii) a pharmaceutically acceptable carrier.

The present invention also relates to a pharmaceutical composition comprising:

(i) an effective amount of an N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere compound for treating alopecia or promoting hair growth in an animal; and

(ii) a pharmaceutically acceptable carrier.

Neurotrophic compounds can be administered with other neurotrophic agents such as neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotropin-3 and neurotropin 4/5. The dosage level of other neurotrophic drugs will depend upon the factors previously stated and the neurotrophic effectiveness of the drug combination.

#### Methods of the Present Invention

The present invention relates to the use of any of the compounds seen in Table I and II and other compounds embodied herein, in the preparation of a medicament for the treatment of a disease such as peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical

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damage to the spinal cord, stroke associated with brain damage, Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis. The present invention also relates to the use of carboxylic acid and carboxylic acid isostere compounds for treating the above-mentioned neuropathies, neurological disorders, and neurological damage.

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The present invention also relates to a method for treating alopecia or promoting hair growth in an animal, which comprises administering to said animal an effective amount of an N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere. The present invention also relates to using the inventive compounds and compositions in the preparation of a medicament for the treatment of alopecia or promoting hair growth in an animal.

15

The inventive method is particularly useful for treating male pattern alopecia, alopecia senilis, alopecia areata, alopecia resulting from skin lesions or tumors, alopecia resulting from cancer therapy such as chemotherapy and radiation, and alopecia resulting from systematic disorders such as nutritional disorders and internal secretion disorders.

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It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the severity of the particular disease or disorder being treated and form of administration.

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#### MPTP Model of Parkinson's Disease in Mice

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MPTP lesioning of dopaminergic neurons in mice is used as an animal model of Parkinson's Disease. Four

week old male CD1 white mice are dosed i.p. with 30 mg/kg of MPTP for 5 days. Test compounds (4 mg/kg), or vehicle, are administered s.c. along with the MPTP for 5 days, as well as for an additional 5 days  
5 following cessation of MPTP treatment. At 18 days following MPTP treatment, the animals are sacrificed and the striata dissected and perfusion-fixed.  
10 Immunostaining is performed on sagittal and coronal brain sections using anti-tyrosine hydroxylase 1 g to quantitate survival and recovery of dopaminergic neurons. In animals treated with MPTP and vehicle, a substantial loss of functional dopaminergic terminals is observed as compared to non-lesioned animals.  
15 Lesioned animals receiving test compounds show a significant recovery of TH-stained dopaminergic neurons. This model presents quantitation for the recovery of TH-positive dopaminergic neurons in the striatum of animals receiving the compounds of the present invention. Table III presents the percent recovery of dopaminergic neurons in the first  
20 (concurrent dosing) paradigm in animals receiving Compound 1, (2S)-1-[(phenylmethyl)sulfonyl]-2-pyrrolidinecarboxylic acid as well related compounds of the present invention.

25 Table III, below, shows the remarkable neuroregenerative effects of carboxylic acid or carboxylic acid isostere related compounds illustrating the neurotrophic capability of carboxylic acid isosteres as a class showing that lesioned  
30 animals receiving the carboxylic acid or carboxylic acid isostere compounds provide a remarkable recovery of TH-stained dopaminergic neurons.

**Table III - MPTP Neurodegenerative Model**

	% Recovery
	Compound A      24.4 %
5	Cmpds B-E      ND
	Compound F      26.7 %
	Compound G      ND
	Compound H      23.2 %
	Compound I      19.6 %
10	Compound J      34.1 %
	Compound K      46.5 %
	Compound L      14.0 %
	Compound M      ND

Percent striatal innervation density was quantitated in brain sections with an anti-tyrosine hydroxylase immunoglobulin, which is indicative of functional dopaminergic neurons. The striatal innervation density of 23% for animals pretreated with only a vehicle and administered a vehicle orally during treatment, is indicative of normal non-lesioned striatal tissue. Striatal innervation density is reduced to 5% for animals pretreated with MPTP and administered a vehicle orally during treatment, and is indicative of MPTP-induced lesioning. Surprisingly, striatal innervation density is increased 8-13% for animals pretreated with MPTP and administered 0.4 mg/kg of compound orally during treatment, indicating substantial neuronal regeneration after induction of MPTP-derived lesions.

**In Vivo Hair Generation Test With C57 Black 6 Mice**

C57 black 6 mice are used to demonstrate the hair revitalizing properties of the ureas and carbamates of N-heterocyclic carboxylic acids or carboxylic acid isosteres. Referring now to FIGS. 1 and 2 of the

drawings, C57 black 6 mice, approximately 7 weeks old,  
had an area of about 2 inches by 2 inches on their  
hindquarters shaved to remove all existing hair. Care  
was taken not to nick or cause abrasion to the  
underlaying dermal layers. The animals were in anagen  
growth phase, as indicated by the pinkish color of the  
skin. Referring now to FIG. 2, four animals per group  
were treated by topical administration with 20%  
propylene glycol vehicle (FIG. 2), or related  
compounds dissolved in the vehicle. The animals were  
treated with vehicle or N-heterocyclic carboxylic  
acids or isosteres every 48 hours (3 applications  
total over the course of 5 days) and the hair growth  
was allowed to proceed for 6 weeks. Hair growth was  
quantitated by the percent of shaved area covered by  
new hair growth during this time period.

FIG. 2 shows that animals treated with vehicle  
exhibited only a small amount of hair growth in  
patches or tufts, with less than 3% of the shaved area  
covered with new growth.

In contrast, FIG. 3 shows that animals treated for 2  
weeks with the N-heterocyclic carboxylic acid  
compounds i.e. compound F, compound G, and compound K  
exhibited dramatic hair growth, covering greater than  
25% of the shaved area in all animals for two of the  
compounds.

FIG. 3 shows the relative hair growth on shaven C57  
black 6 mice 14 days after being treated with N-  
heterocyclic carboxylic acids or carboxylic acid  
isosteres. The mice had a 2 x 2 inch region on their  
backside shaved to remove all hair. Care was taken  
not to nick or cause abrasion to the underlying dermal  
layers. Compounds at a concentration of 1  $\mu$ mole per  
milliliter were carefully applied to the shaved area  
of the mice (5 mice per group) three times per week.

Hair growth was evaluated 14 days after initiation of drug treatment. The relative scale for assessing hair growth is as follows:

0 = no growth;

5 1 = beginning of growth in small tufts;

2 = hair growth covering over <25% of shaved area;

10 3 = hair growth covering over >25% of shaved area, but less than 50% of shaved area;

4 = hair growth covering over >50% of shaved area, but less than 75% of shaved area;

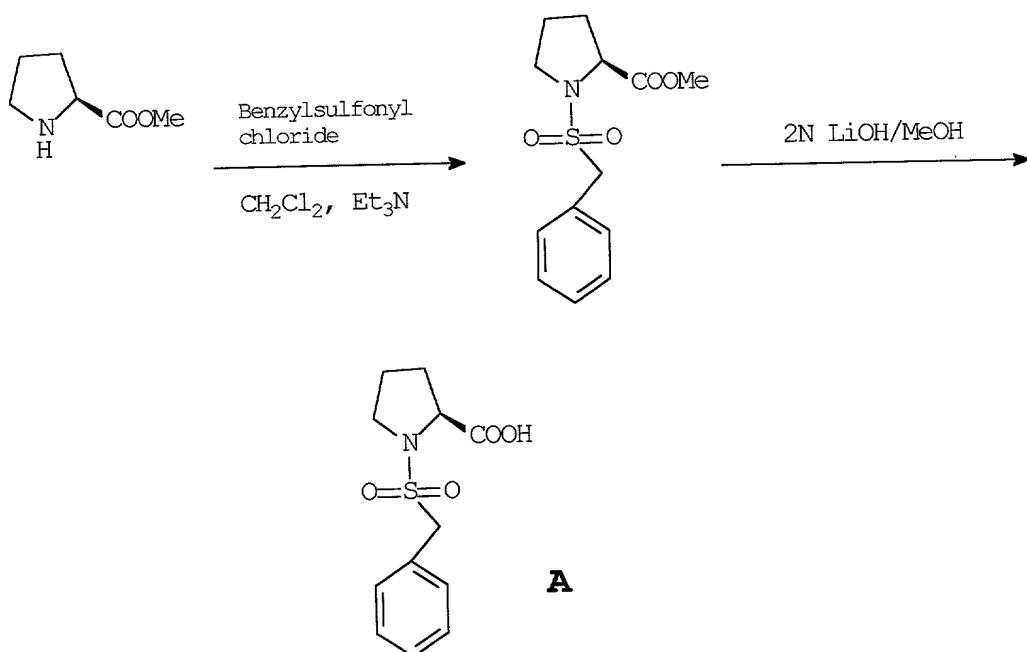
15 5 = complete hair growth of shaved area.

The following examples are illustrative of preferred embodiments of the invention and are not to be construed as limiting the invention thereto. All polymer molecular weights are mean average molecular weights. All percentages are based on the percent by weight of the final delivery system or formulation prepared unless otherwise indicated and all totals equal 100% by weight.

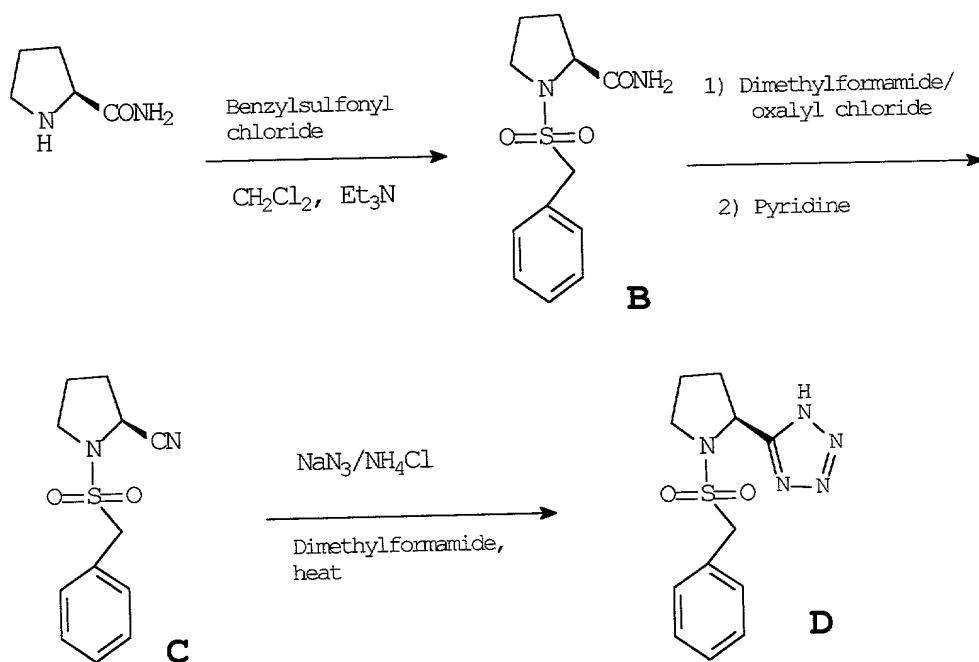
#### EXAMPLES

The inventive compounds may be prepared by a variety of synthetic sequences that utilize established chemical transformations. An exemplary general pathway to the present compounds is described in Scheme I, Scheme II, and Scheme III.

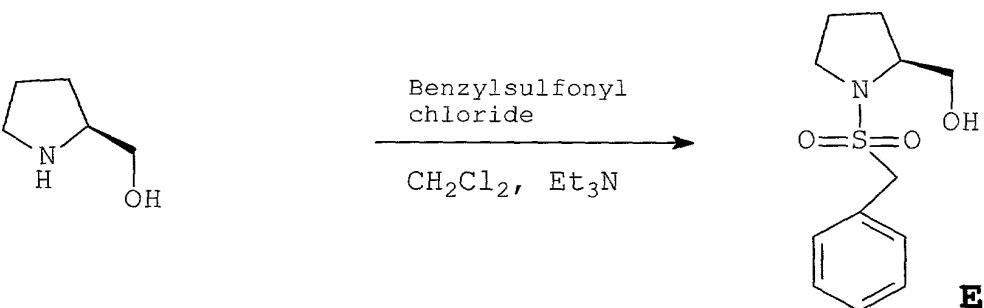
SCHEME I



SCHEME II



**SCHEME III**



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**EXAMPLE 1**

Synthesis of (2S)-N-(benzylsulfonyl)-2-pyrrolidinecarboxylic acid (Table I Compound 1) (Table II and Scheme I Compound A)

To a cooled (0°C) solution of proline methyl ester hydrochloride salt (5.0 g; 30.19 mmol) in 200 mL of methylene chloride was added triethylamine (35mL) and benzenesulfonyl chloride (5.75 g; 30.19 mmol). The mixture was stirred for one hour at 0°C and then washed with 2 x 100 mL of water. The organic phase was dried and concentrated. Chromatography eluting with 50% EtOAc/hexane delivered 8.14 g (5%) of the N-sulfonamide methyl ester, which was dissolved in 120 mL of methanol, cooled to 0°C, and treated with 40 mL of 1 N lithium hydroxide. The mixture was stirred for 1 hour at 0°C and then overnight at room temperature. After making the reaction mixture acidic (pH 1) with 1 N HCl, the product was extracted into methylene chloride and dried and concentrated to yield 4.25 g of (2S)-N-(benzylsulfonyl)-2-pyrrolidinecarboxylic acid (A) as a white solid, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 1.85-1.90 (m, 2H); 2.08 (m, 1H); 2.18 (m, 1H); 3.04 (m, 1H); 3.27 (m, 1H); 4.32-4.35 (m, 2H); 4.45 (m, 1H); 4.45 (m, 2H); 7.36 (m, 3H); 7.48 (m, 2H); 10.98 (br, 1H).

20

**EXAMPLE 2**

Synthesis of (2S)-1-(phenylmethylsulfonyl)-2-hydroxymethyl pyrrolidine (Compound 95) (Scheme III Compound E).

To a solution of (S)-(+)-2-pyrrolidinemethanol (1.01 g, 10 mmol) and triethylamine (1.5 ml, 11 mmol) in 30 ml methylene chloride was added 1.9 g (10 mmol)  $\alpha$ -toluenesulfonyl chloride at 0°C with stirring. The reaction was gradually warmed up to room temperature and stirred overnight. The mixture was diluted with water, and extracted into 200 ml methylene chloride. The organic extract was concentrated and further purified by silica gel to give 1.5 g product as a white solid (58.9% yield).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  01.71-1.88 (m, 4H); 2.05 (br, 1H, OH); 3.22 (m, 2H); 3.47 (m, 2H); 3.67 (m, 1H); 4.35 (s, 2H); 7.26-7.44 (m, 5H, aromatic).

**EXAMPLE 3**

Synthesis of (2S)-1-(phenylmethyl)sulfonyl-2-pyrrolidinecarboxamide (Compound 96) (Scheme II Compound B).

To a solution of L-prolinamide (2.28 g, 20 mmol) and triethylamine (5.76 ml, 42 mmol) in 40 ml methylene chloride was added 3.92 g (20 mmol)  $\alpha$ -toluenesulfonyl chloride at 0°C with stirring. The reaction was gradually warmed up to room temperature and stirred overnight. The mixture was diluted with water, and extracted into 200 ml methylene chloride. The organic extract was concentrated and further purified by silica gel to give 3.0 g product as a white solid (55.7% yield).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  01.89 (m, 3H); 2.25 (m, 1H); 3.40 (m, 1H); 3.50 (m, 1H); 3.96 (m, 1H); 4.35 (s, 2H); 7.39-7.45 (m, 5H, aromatic).

**EXAMPLE 4**

Synthesis of (2S)-1-(phenylmethyl)sulfonyl-2-pyrrolidinecarbonitrile (Compound 97) (Scheme II Compound C).

To a solution of 0.67 ml DMF (8.7 mmol) in 10 ml acetonitrile at 0°C was added 0.70 ml (8.0 mmol) oxalyl chloride. A white precipitate was formed immediately and was accompanied by gas evolution. When complete, a solution of 2.0 g (7.5 mmol) of (2S)-1-(phenylmethyl)sulfonyl-2-pyrrolidinecarboxamide in 5.0 ml acetonitrile was added. When the mixture became homogeneous, 1.35 ml (16.5 mmol) pyridine was added. After 5 min., the mixture was diluted with water, and extracted by 200 ml ethyl acetate. The organic layer was concentrated and further purified by silica gel to give 1.5 g product as a white solid (80% yield).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): d 01.92 (m, 2H); 2.01 (m, 1H); 2.11 (m, 1H); 3.45 (m, 2H); 4.35 (s, 2H); 4.65 (m, 1H); 7.26-7.45 (m, 5H, aromatic).

**EXAMPLE 5**

Synthesis of (2S)-1-(phenylmethyl)sulfonyl-2-pyrrolidinetetrazole (Compound 4) (Scheme II Compound D).

A mixture of (2S)-1-(phenylmethyl)sulfonyl-2-pyrrolidinecarbonitrile (250 mg, 1 mmol),  $\text{NaN}_3$  (81 mg, 1.3 mmol) and  $\text{NH}_4\text{Cl}$  (70 mg, 1.3 mmol) in 3 ml DMF was stirred at 130°C for 16 hours. The mixture was concentrated and purified by silica gel to give 120 mg product as a white solid (41.1% yield).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): d 01.95 (m, 2H); 2.21 (m, 1H); 2.90 (m, 1H); 3.40 (m, 2H); 4.27 (s, 2H); 5.04 (m, 1H); 7.36-7.41 (m, 5H, aromatic); 8.05 (s, 1H, NH).

**Example 6**

A lotion comprising the following composition may be

prepared.

	(%)
5	95% Ethanol 80.0
	an N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere 10.0
	$\alpha$ -Tocopherol acetate 0.01
	Ethylene oxide (40 mole) adducts of hardened castor oil 0.5
10	purified water 9.0
	perfume and dye q.s.

Into 95% ethanol are added an N-linked sulfonamides of N-heterocyclic carboxylic acid or carboxylic acid isostere,  $\alpha$ -tocopherol acetate, ethylene oxide (40 mole) adducts of hardened castor oil, perfume and a dye. The resulting mixture is stirred and dissolved, and purified water is added to the mixture to obtain a transparent liquid lotion.

5 ml of the lotion may be applied once or twice per day to a site having marked baldness or alopecia.

**Example 7**

A lotion comprising the following composition shown may be prepared.

	(%)
25	95% Ethanol 80.0
	an N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere 0.005
	Hinokitol 0.01
30	Ethylene oxide (40 mole) adducts of hardened castor oil 0.5
	Purified water 19.0
	Perfume and dye q.s.

5            Into 95% ethanol are added an N-linked sulfonamides  
of N-heterocyclic carboxylic acid or carboxylic acid  
isostere, hinokitol, ethylene oxide (40 mole) adducts  
of hardened castor oil, perfume, and a dye. The  
resulting mixture is stirred, and purified water is  
added to the mixture to obtain a transparent liquid  
lotion.

10          The lotion may be applied by spraying once to 4  
times per day to a site having marked baldness or  
alopecia.

**Example 8**

An emulsion may be prepared from A phase and B phase  
having the following compositions.

<b>(A phase)</b>		(%)
Whale wax		0.5
Cetanol		2.0
Petrolatum		5.0
Squalane		10.0
Polyoxyethylene (10 mole) monostearate		2.0
Sorbitan monooleate		1.0
an N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere		0.01
<b>(B phase)</b>		(%)
Glycerine		10.0
Purified water		69.0
Perfume, dye, and preservative		q.s.

30          The A phase and the B phase are respectively heated  
and melted and maintained at 80°C. Both phases are  
then mixed and cooled under stirring to normal  
temperature to obtain an emulsion.

The emulsion may be applied by spraying once to 4

times per day to a site having marked baldness or alopecia.

**Example 9**

A cream may be prepared from A phase and B phase having the following compositions.

(A Phase)		(%)
Fluid paraffin		5.0
Cetostearyl alcohol		5.5
Petrolatum		5.5
Glycerine monostearate		33.0
Polyoxyethylene (20 mole) 2-octyldodecyl ether		3.0
Propylparaben		0.3
(B Phase)		(%)
an N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere		0.8
Glycerine		7.0
Dipropylene glycol		20.0
Polyethylene glycol 4000		5.0
Sodium Hexametaphosphate		0.005
Purified water		44.895

The A phase is heated and melted, and maintained at 70°C. The B phase is added into the A phase and the mixture is stirred to obtain an emulsion. The emulsion is then cooled to obtain a cream.

The cream may be applied once to 4 times per day to a site having marked baldness or alopecia.

**Example 10**

A liquid comprising the following composition may be prepared.

	(%)
Polyoxyethylene butyl ether	20.0
Ethanol	50.0
an N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere	0.001
Propylene glycol	5.0
Polyoxyethylene hardened castor oil derivative (ethylene oxide 80 mole adducts)	0.4
Perfume	q.s.
Purified water	q.s.

Into ethanol are added polyoxypropylene butyl ether, propylene glycol, polyoxyethylene hardened castor oil, an N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere, and perfume. The resulting mixture is stirred, and purified water is added to the mixture to obtain a liquid.

The liquid may be applied once to 4 times per day to a site having marked baldness or alopecia.

#### Example 11

A shampoo comprising the following composition may be prepared.

	(%)
Sodium laurylsulfate	5.0
Triethanolamine laurylsulfate	5.0
Betaine lauryldimethylaminoacetate	6.0
Ethylene glycol distearate	2.0
Polyethylene glycol	5.0
an N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere	5.0

Ethanol	2.0
Perfume	0.3
Purified water	69.7

5           Into 69.7 g of purified water are added 5.0 g of sodium laurylsulfate, 5.0 g of triethanolamine laurylsulfate, 6.0 g of betaine lauryldimethyl-aminoacetate. Then a mixture obtained by adding 5.0 g of an N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere, 5.0 g of polyethylene glycol, and 2.0 g of ethylene glycol distearate to 2.0 g of ethanol, followed by stirring, and 0.3 g of perfume are successively added. The resulting mixture is heated and subsequently cooled to obtain a shampoo.

10           The shampoo may be used on the scalp once or twice per day.

#### Example 12

15           A patient is suffering from alopecia senilis. An N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

#### Example 13

20           A patient is suffering from male pattern alopecia. An N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere, or a pharmaceutical composition comprising the same may be administered to the patient. Increased hair growth is expected to occur following treatment.

#### Example 14

25           A patient is suffering from alopecia areata. An N-linked sulfonamide of N-heterocyclic carboxylic acid or

carboxylic acid isostere, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

5

**Example 15**

A patient is suffering from hair loss caused by skin lesions. An N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

10

**Example 16**

A patient is suffering from hair loss caused by tumors. An N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

15

**Example 17**

A patient is suffering from hair loss caused by a systematic disorder, such as a nutritional disorder or an internal secretion disorder. An N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

20

25

**Example 18**

A patient is suffering from hair loss caused by chemotherapy. An N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

30

**Example 19**

A patient is suffering from hair loss caused by radiation. An N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere, or a pharmaceutical composition comprising the same may, be administered to the patient. Increased hair growth is expected to occur following treatment.

**Example 20**

A patient is suffering from a neurodegenerative disease. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or a pharmaceutical composition comprising the same is administered. It would be expected that the patient would improve their condition or recover.

**Example 21**

A patient is suffering from a neurological disorder. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

**Example 22**

A patient is suffering from stroke. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

**Example 23**

A patient is suffering from Parkinson's Disease. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

**Example 24**

A patient is suffering from Alzheimer's Disease. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

**Example 25**

A patient is suffering from a peripheral neuropathy. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

**Example 26**

A patient is suffering from amyotrophic lateral sclerosis. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

**Example 27**

A patient is suffering from a spinal injury. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

**Example 28**

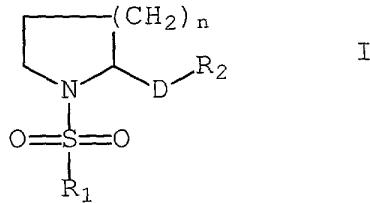
A patient is at risk of suffering from a neurodegenerative disease or neurological disorder. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or a pharmaceutical composition comprising the same is prophelactically administered.

It would be expected that the patient would be prevented from some or all of the effects of the disease or disorder, or would significantly improve their condition or recover over patients who were not pre-treated.

5       The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modification are intended to be included within the  
10      scope of the following claims.

What is claimed is:

1. A compound having the formula (I):



5

where

n is 1-3;

R<sub>1</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>9</sub> straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, or heterocycle;

D is a bond, or a C<sub>1</sub>-C<sub>10</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>10</sub> alkynyl;

R<sub>2</sub> is a carboxylic acid or a carboxylic acid isostere; wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or carboxylic acid isostere is optionally substituted with one or more substituents selected from R<sup>3</sup>, where

R<sup>3</sup> is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulphydryl, thioalkyl, alkylthio, sulfonyl, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO<sub>2</sub>R<sup>4</sup> where R<sup>4</sup> is hydrogen or C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl or alkenyl;

or a pharmaceutically acceptable salt, ester or solvate thereof;

provided that:

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when D is a bond, and R<sub>2</sub> is COOH,  
then R<sub>1</sub> cannot be substituted naphthyl;  
further provided that:  
when D is a bond, and n is 1, and R<sub>2</sub> is COOH or CONHR<sub>3</sub>,  
then R<sub>1</sub> is not hydroxyl, methyl, ethyl, substituted or  
unsubstituted thioethyl, benzothiazole, substituted  
benzopyran, substituted benzopyrrole, substituted  
benzoxazole, substituted 5-membered heterocycle  
containing two N and one S heteroatoms, or substituted  
or unsubstituted phenyl, phenylethyl, naphthyl, pyridyl,  
thienyl, quinoline, tricyclic ring, aminoethyl, or  
benzyl;  
further provided that:  
when D is a bond, and n is 2, and R<sub>2</sub> is COOH or  
phenylbutyl ester,  
then R<sub>1</sub> is not substituted phenyl, or a substituted  
bicyclic ring containing two oxygen heteroatoms.  
further provided that:  
when D is a bond, and n is 1-2, and R<sub>2</sub> is a substituted  
or unsubstituted carbocyclic or heterocyclic ring  
structure,  
then R<sub>1</sub> is not substituted or unsubstituted carbocycle  
or heterocycle, or hydroxy;  
further provided that:  
when D is a bond, and n is 1-2, and R<sub>2</sub> is hydroxy,  
alkoxy, -SO<sub>2</sub>(phenyl), N(R<sub>3</sub>)<sub>2</sub>, substituted thio or  
alkylthio, -NCO, -PO<sub>3</sub>(Me)<sub>2</sub>, or -NCOOC(ethyl)phenyl,  
then R<sub>1</sub> is not naphthalene, ethylene, substituted  
tricyclic ring, or substituted or unsubstituted phenyl;  
further provided that:  
when D is C<sub>1</sub>-C<sub>3</sub> alkyl or hexenyl, and R<sub>2</sub> is hydroxyl,  
then R<sub>1</sub> is not substituted or unsubstituted phenyl, or  
benzoimidazole;  
further provided that:  
when D is methyl, and n is 1, and R<sub>2</sub> is cyano or COOH,

then R<sub>1</sub> is not substituted phenyl;

further provided that:

when D is methyl, and n is 1, and R<sub>2</sub> is methoxy or N(R<sub>3</sub>)<sub>2</sub>,

5 then R<sub>1</sub> is not methyl, ethyl, phenylethyl, chloro substituted alkyl, substituted oxirane, substituted aziridine wherein one of the carbons is replaced with an oxygen, substituted or unsubstituted propenyl, substituted phenyl, benzyl, or trifluoro substituted C<sub>2</sub>-C<sub>3</sub> alkyl or alkenyl;

further provided that:

when D is ethyl, and n is 2, and R<sub>2</sub> is hydroxyl or N(R<sub>3</sub>)<sub>2</sub>,

10 then R<sub>1</sub> is not naphthyl;

further provided that:

when D is propyl, and n is 1, and R<sub>2</sub> is methoxy,

15 then R<sub>1</sub> is not ethylene, cyano substituted ethyl, or triethoxy substituted propyl;

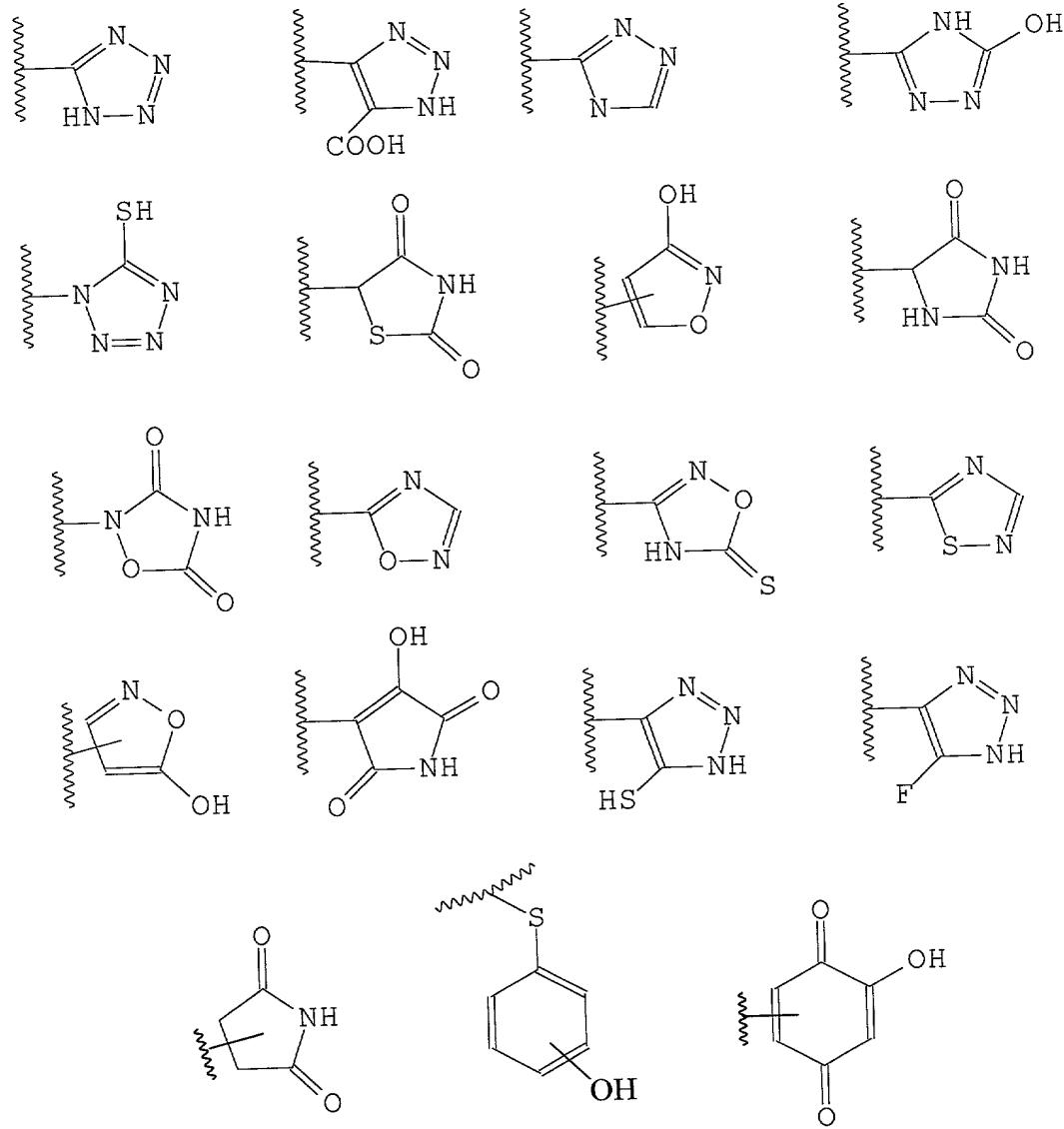
further provided that:

20 when D is not a bond and at least one of D and R<sub>2</sub> contains at least one S or O,

then R<sub>1</sub> is not methyl or substituted phenyl.

25 2. The compound of claim 1, wherein R<sub>2</sub> is a carbocycle or heterocycle containing any combination of CH<sub>2</sub>, O, S, or N in any chemically stable oxidation state, wherein any of the atoms of said ring structure are optionally substituted in one or more positions with R<sup>3</sup>.

30 3. The compound of claim 1, wherein R<sub>2</sub> is selected from the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R<sup>3</sup>.

4. The compound of claim 1, wherein the carboxylic acid or carboxylic acid isostere of R<sub>2</sub> is selected from the group consisting of:

-COOH, -SO<sub>3</sub>H, -SO<sub>2</sub>HNR<sup>3</sup>, -PO<sub>2</sub>(R<sup>3</sup>)<sub>2</sub>, -CN, -PO<sub>3</sub>(R<sup>3</sup>)<sub>2</sub>, -OR<sup>3</sup>, -SR<sup>3</sup>, -NHCOR<sup>3</sup>, -N(R<sup>3</sup>)<sub>2</sub>, -CON(R<sup>3</sup>)<sub>2</sub>, -CONH(O)R<sup>3</sup>, -CONHNHSO<sub>2</sub>R<sup>3</sup>, -COHNSO<sub>2</sub>R<sup>3</sup>, and -CONR<sup>3</sup>CN.

10

5. The compounds, (2S)-1-(phenylmethyl)sulfonyl-2-hydroxymethyl pyrrolidine; (2S)-1-(phenylmethyl)sulfonyl-2-pyrrolidinetetrazole.

15

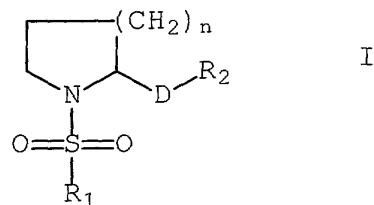
6. A pharmaceutical composition, comprising:

- a) an effective amount of an N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere; and
- b) a pharmaceutically acceptable carrier.

20

7. The pharmaceutical composition of claim 6, wherein the N-linked sulfonamide of N-heterocyclic carboxylic acid or carboxylic acid isostere comprises a compound of formula (I):

25



where

n is 1-3;

R<sub>1</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>9</sub> straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, or heterocycle;

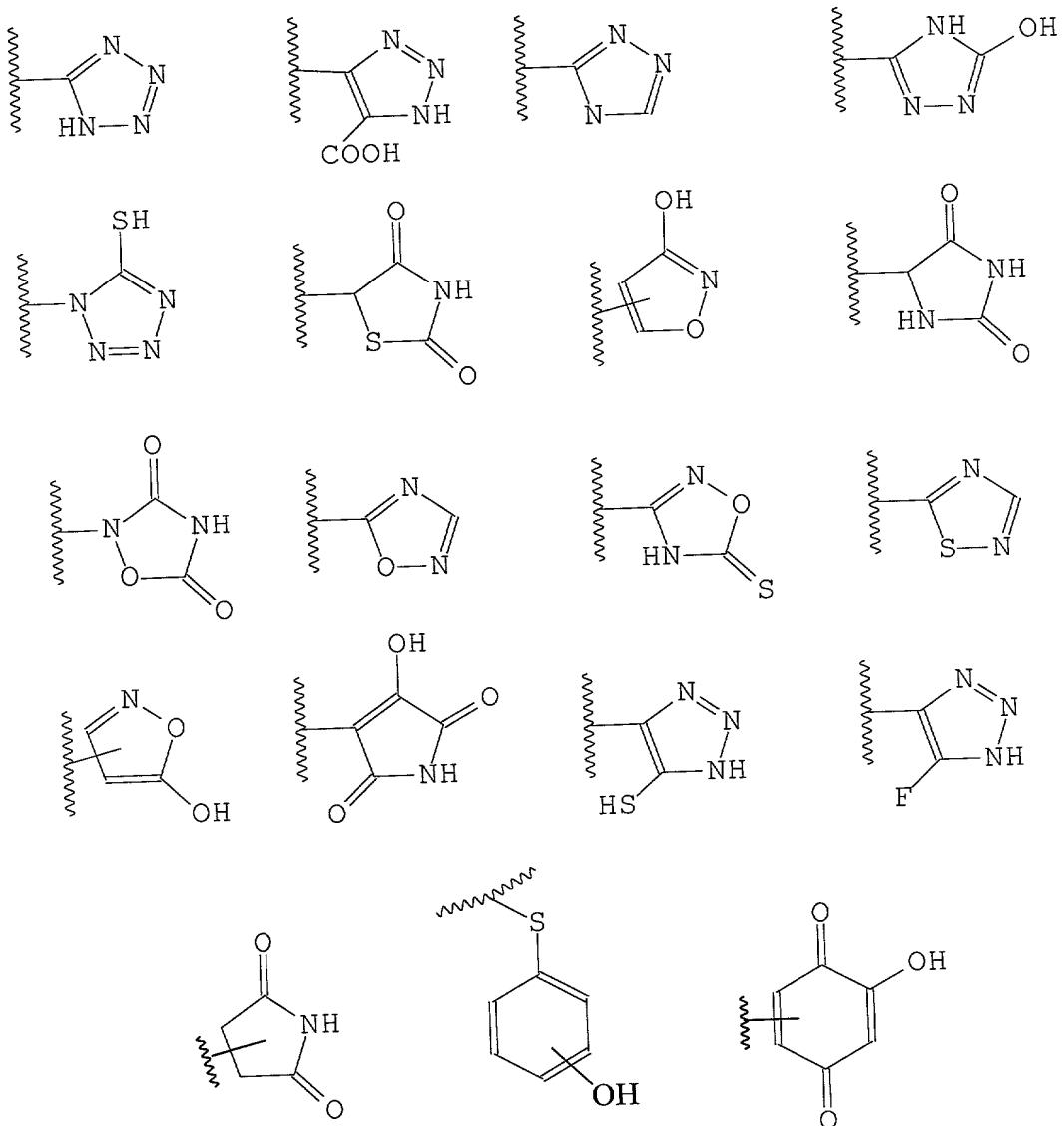
5 D is a bond, or a C<sub>1</sub>-C<sub>10</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>10</sub> alkynyl;

R<sub>2</sub> is a carboxylic acid or a carboxylic acid isostere; wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or carboxylic acid isostere is 10 optionally substituted with one or more substituents selected from R<sup>3</sup>, where

R<sup>3</sup> is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulphydryl, thioalkyl, alkylthio, sulfonyl, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO<sub>2</sub>R<sup>4</sup> where R<sup>4</sup> is hydrogen or C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl or alkenyl; 15 or a pharmaceutically acceptable salt, ester or solvate thereof.

20 8. The pharmaceutical composition of claim 7, wherein R<sub>2</sub> is a carbocycle or heterocycle containing any combination of CH<sub>2</sub>, O, S, or N in any chemically stable oxidation state, wherein any of the atoms of said ring structure are optionally substituted in one or more positions with R<sup>3</sup>.

25 30 9. The pharmaceutical composition of claim 7, wherein R<sub>2</sub> is selected from the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R<sup>3</sup>.

10. The pharmaceutical composition of claim 7, wherein  
5 R<sub>2</sub> is selected from the group consisting of:

-COOH, -SO<sub>3</sub>H, -SO<sub>2</sub>HNR<sup>3</sup>, -PO<sub>2</sub>(R<sup>3</sup>)<sub>2</sub>, -CN, -PO<sub>3</sub>(R<sup>3</sup>)<sub>2</sub>, -OR<sup>3</sup>, -SR<sup>3</sup>, -NHCOR<sup>3</sup>, -N(R<sup>3</sup>)<sub>2</sub>, -CON(R<sup>3</sup>)<sub>2</sub>, -CONH(O)R<sup>3</sup>,  
-CONHNHSO<sub>2</sub>R<sup>3</sup>, -COHNSO<sub>2</sub>R<sup>3</sup>, and -CONR<sup>3</sup>CN.

10. The pharmaceutical composition of claim 7, wherein  
10 the N-linked sulfonamide of an N-heterocyclic carboxylic acid compound is selected from the group consisting of compounds 1-97.

15. The pharmaceutical composition of claim 6, further comprising a neurotrophic factor different from formula (I).

20. The pharmaceutical composition of claim 12, wherein said neurotrophic factor different from formula (I) is selected from neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotropin-3 and neurotropin 4/5.

25. A method of treating a neurological disorder in an animal, comprising:

30. administering to the animal an effective amount of an N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere to stimulate growth of damaged peripheral nerves or to promote neuronal regeneration.

15. The method of claim 14, wherein the neurological disorder is selected from the group consisting of peripheral neuropathies cause by physical injury or disease state, physical damage to the brain, physical  
5 damage to the spinal cord, stroke associated with brain damage, and neurological disorders relating to neurodegeneration.

10 16. The method of claim 14, wherein the neurological disorder is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

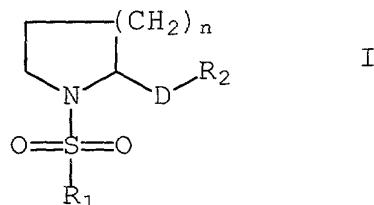
15 17. The method of claim 14, wherein the neurological disorder is Alzheimer's disease.

20 18. The method of claim 14, wherein the neurological disorder is Parkinson's disease.

25 19. The method of claim 14, wherein the neurological disorder is amyotrophic lateral sclerosis.

20 20. The method of claim 14, wherein the N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere is non-immunosuppressive.

30 21. The method of claim 14, wherein the N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere comprises a compound of formula (I):



where

n is 1-3;

R<sub>1</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>9</sub> straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, or heterocycle;

D is a bond, or a C<sub>1</sub>-C<sub>10</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>10</sub> alkynyl;

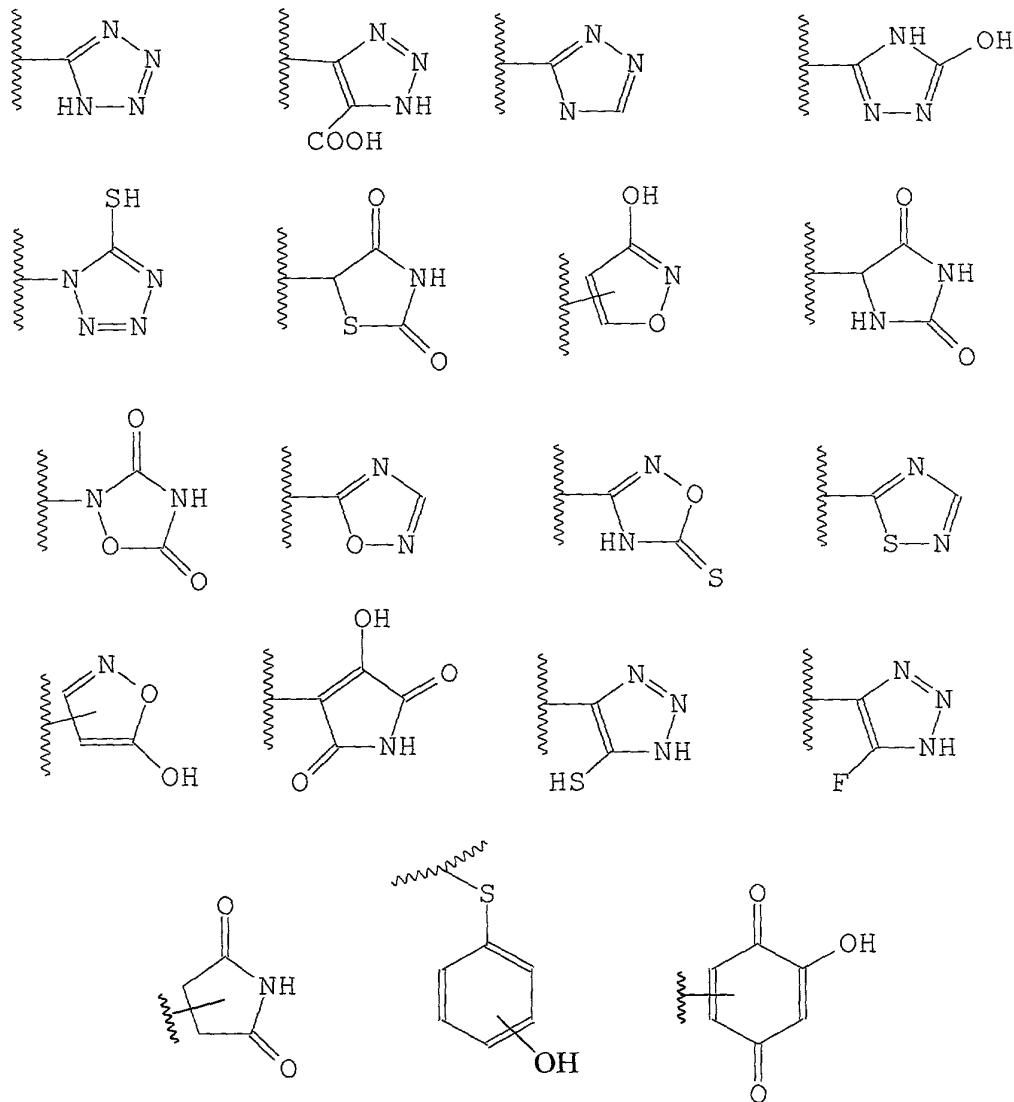
R<sub>2</sub> is a carboxylic acid or a carboxylic acid isostere; wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or carboxylic acid isostere is optionally substituted with one or more substituents selected from R<sup>3</sup>, where

R<sup>3</sup> is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulphydryl, thioalkyl, alkylthio, sulfonyl, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO<sub>2</sub>R<sup>4</sup> where R<sup>4</sup> is hydrogen or C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl or alkenyl; or a pharmaceutically acceptable salt, ester or solvate thereof.

22. The method of claim 21, wherein R<sub>2</sub> is a carbocycle or heterocycle containing any combination of CH<sub>2</sub>, O, S, or N in any chemically stable oxidation state, wherein

any of the atoms of said ring structure are optionally substituted in one or more positions with R<sup>3</sup>.

23. The method of claim 21, wherein R<sub>2</sub> is selected from  
5 the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R<sup>3</sup>.

24. The method of claim 21, wherein R<sub>2</sub> is selected from  
the group consisting of:  
5 -COOH, -SO<sub>3</sub>H, -SO<sub>2</sub>HNR<sup>3</sup>, -PO<sub>2</sub>(R<sup>3</sup>)<sub>2</sub>, -CN, -PO<sub>3</sub>(R<sup>3</sup>)<sub>2</sub>, -OR<sup>3</sup>, -SR<sup>3</sup>, -NHCOR<sup>3</sup>, -N(R<sup>3</sup>)<sub>2</sub>, -CON(R<sup>3</sup>)<sub>2</sub>, -CONH(O)R<sup>3</sup>, -CONHNHSO<sub>2</sub>R<sup>3</sup>, -COHNSO<sub>2</sub>R<sup>3</sup>, and -CONR<sup>3</sup>CN.

10 25. The method of claim 14, wherein the N-linked sulfonamide of an N-heterocyclic carboxylic acid compound is selected from the group consisting of compounds 1-97.

15 26. The method of claim 14, further comprising administering a neurotrophic factor different from formula (I).

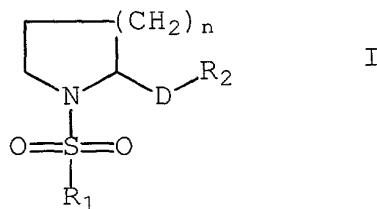
20 27. The method of claim 26, wherein said neurotrophic factor different from formula (I) is selected from the group consisting of neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotropin-3, and neurotropin 4/5.  
25

30 28. A method of stimulating growth of damaged peripheral nerves, comprising:  
35 administering to damaged peripheral nerves a therapeutically effective amount of an N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere to stimulate or promote growth

of the damaged peripheral nerves.

29. The method of claim 28, wherein the N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere is non-immunosuppressive.

30. The method of claim 28, wherein the N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere comprises a compound of formula 10 (I):



where

n is 1-3;

R<sub>1</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>9</sub> straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, or heterocycle;

D is a bond, or a C<sub>1</sub>-C<sub>10</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>10</sub> alkynyl;

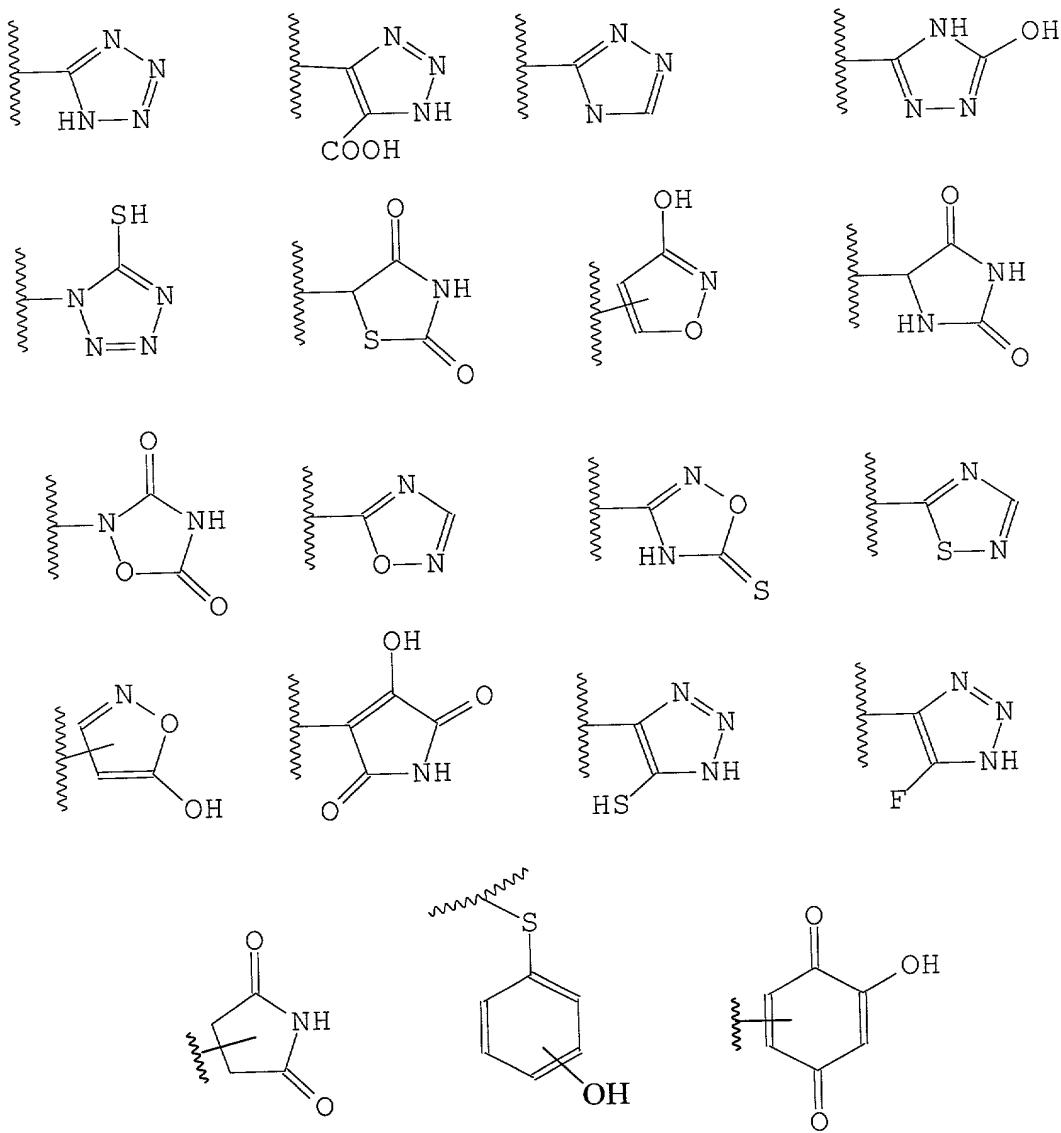
R<sub>2</sub> is a carboxylic acid or a carboxylic acid isostere; wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or carboxylic acid isostere is optionally substituted with one or more substituents selected from R<sup>3</sup>, where

R<sup>3</sup> is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulphydryl, thioalkyl, alkylthio, sulfonyl, C<sub>1</sub>-C<sub>6</sub> straight or

branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain  
alkenyl or alkynyl, aryl, heteroaryl, carbocycle,  
heterocycle, or CO<sub>2</sub>R<sup>4</sup> where R<sup>4</sup> is hydrogen or C<sub>1</sub>-C<sub>9</sub>  
straight or branched chain alkyl or alkenyl;  
5 or a pharmaceutically acceptable salt, ester or solvate  
thereof.

31. The method of claim 30, wherein R<sub>2</sub> is a carbocycle  
or heterocycle containing any combination of CH<sub>2</sub>, O, S,  
10 or N in any chemically stable oxidation state, wherein  
any of the atoms of said ring structure are optionally  
substituted in one or more positions with R<sup>3</sup>.

32. The method of claim 30, wherein R<sub>2</sub> is selected from  
15 the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R<sup>3</sup>.

33. The method of claim 30, wherein R<sub>2</sub> is selected from the group consisting of:

5 -COOH, -SO<sub>3</sub>H, -SO<sub>2</sub>HNR<sup>3</sup>, -PO<sub>2</sub>(R<sup>3</sup>)<sub>2</sub>, -CN, -PO<sub>3</sub>(R<sup>3</sup>)<sub>2</sub>, -OR<sup>3</sup>, -SR<sup>3</sup>, -NHCOR<sup>3</sup>, -N(R<sup>3</sup>)<sub>2</sub>, -CON(R<sup>3</sup>)<sub>2</sub>, -CONH(O)R<sup>3</sup>, -CONHNHSO<sub>2</sub>R<sup>3</sup>, -COHNSO<sub>2</sub>R<sup>3</sup>, and -CONR<sup>3</sup>CN.

10 34. The method of claim 28, wherein the N-linked sulfonamide of an N-heterocyclic carboxylic acid compound is selected from the group consisting of compounds 1-97.

15 35. The method of claim 28, further comprising administering a neurotrophic factor different from formula (I).

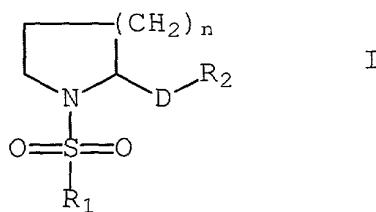
20 36. The method of claim 35, wherein said neurotrophic factor different from formula (I) is selected from the group consisting of neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotropin-3, and neurotropin 4/5.

25 37. A method for promoting neuronal regeneration and growth in animals, comprising:

30 administering to an animal a therapeutically effective amount of a neurotrophic N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere to promote neuronal regeneration.

38. The method of claim 37, wherein the N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere is non-immunosuppressive.

5       39. The method of claim 37, wherein the N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere comprises a compound of formula (I):



10 where

n is 1-3;

R<sub>1</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>9</sub> straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, or heterocycle;

D is a bond, or a C<sub>1</sub>-C<sub>10</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>10</sub> alkynyl;

R<sub>2</sub> is a carboxylic acid or a carboxylic acid isostere; wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or carboxylic acid isostere is optionally substituted with one or more substituents selected from R<sup>3</sup>, where

R<sup>3</sup> is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, alkylthio, sulfonyl, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle,

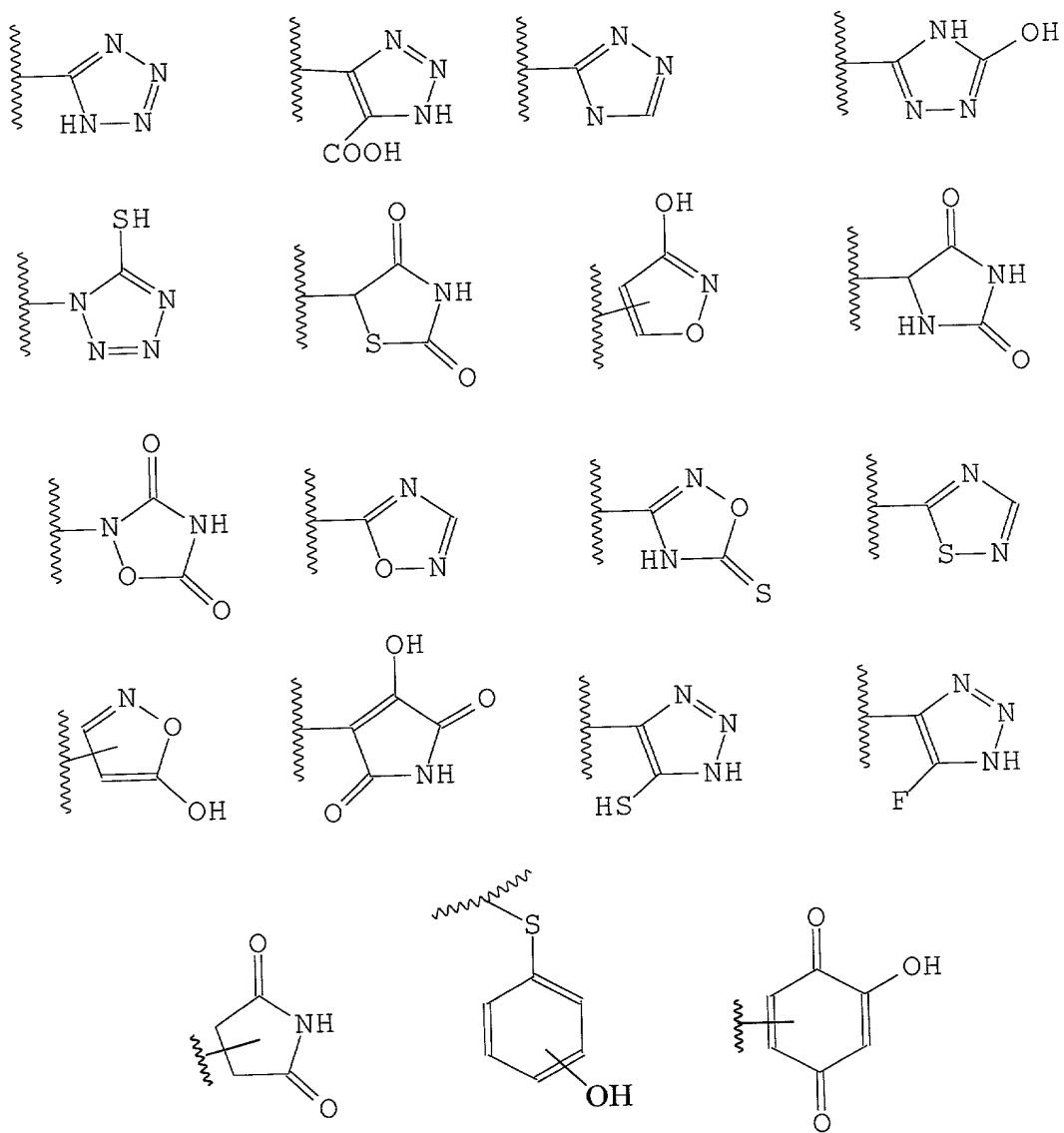
heterocycle, or  $\text{CO}_2\text{R}^4$  where  $\text{R}^4$  is hydrogen or  $\text{C}_1\text{-C}_9$  straight or branched chain alkyl or alkenyl; or a pharmaceutically acceptable salt, ester or solvate thereof.

5

40. The method of claim 39, wherein  $\text{R}_2$  is a carbocycle or heterocycle containing any combination of  $\text{CH}_2$ , O, S, or N in any chemically stable oxidation state, wherein any of the atoms of said ring structure are optionally substituted in one or more positions with  $\text{R}^3$ .

10

41. The method of claim 39, wherein  $\text{R}_2$  is selected from the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R<sup>3</sup>.

42. The method of claim 39, wherein R<sub>2</sub> is selected from the group consisting of:

-COOH, -SO<sub>3</sub>H, -SO<sub>2</sub>HNR<sup>3</sup>, -PO<sub>2</sub>(R<sup>3</sup>)<sub>2</sub>, -CN, -PO<sub>3</sub>(R<sup>3</sup>)<sub>2</sub>, -OR<sup>3</sup>, -SR<sup>3</sup>, -NHCOR<sup>3</sup>, -N(R<sup>3</sup>)<sub>2</sub>, -CON(R<sup>3</sup>)<sub>2</sub>, -CONH(O)R<sup>3</sup>, -CONHNHSO<sub>2</sub>R<sup>3</sup>, -COHNSO<sub>2</sub>R<sup>3</sup>, and -CONR<sup>3</sup>CN.

43. The method of claim 37, wherein the N-linked sulfonamide of an N-heterocyclic carboxylic acid compound is selected from the group consisting of compounds 1-97.

44. The method of claim 37, further comprising administering a neurotrophic factor different from formula (I).

45. The method of claim 44, wherein said neurotrophic factor different from formula (I) is selected from the group consisting of neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotropin-3, and neurotropin 4/5.

46. A method for preventing neurodegeneration in an animal, comprising:

administering to an animal a therapeutically effective amount of a neurotrophic N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere to prevent neurodegeneration.

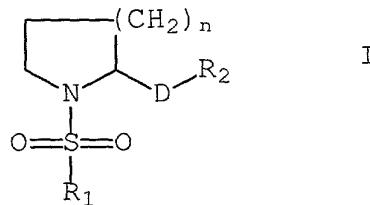
47. The method of claim 46, wherein the neurodegeneration is Alzheimer's disease.

5 48. The method of claim 46, wherein the neurodegeneration is Parkinson's disease.

49. The method of claim 46, wherein the neurodegeneration is amyotrophic lateral sclerosis.

10 50. The method of claim 46, wherein the N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere is non-immunosuppressive.

15 51. The method of claim 46, wherein the N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere comprises a compound of formula (I):



where

20 n is 1-3;

R<sub>1</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>9</sub> straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, or heterocycle;

25 D is a bond, or a C<sub>1</sub>-C<sub>10</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>10</sub> alkynyl;

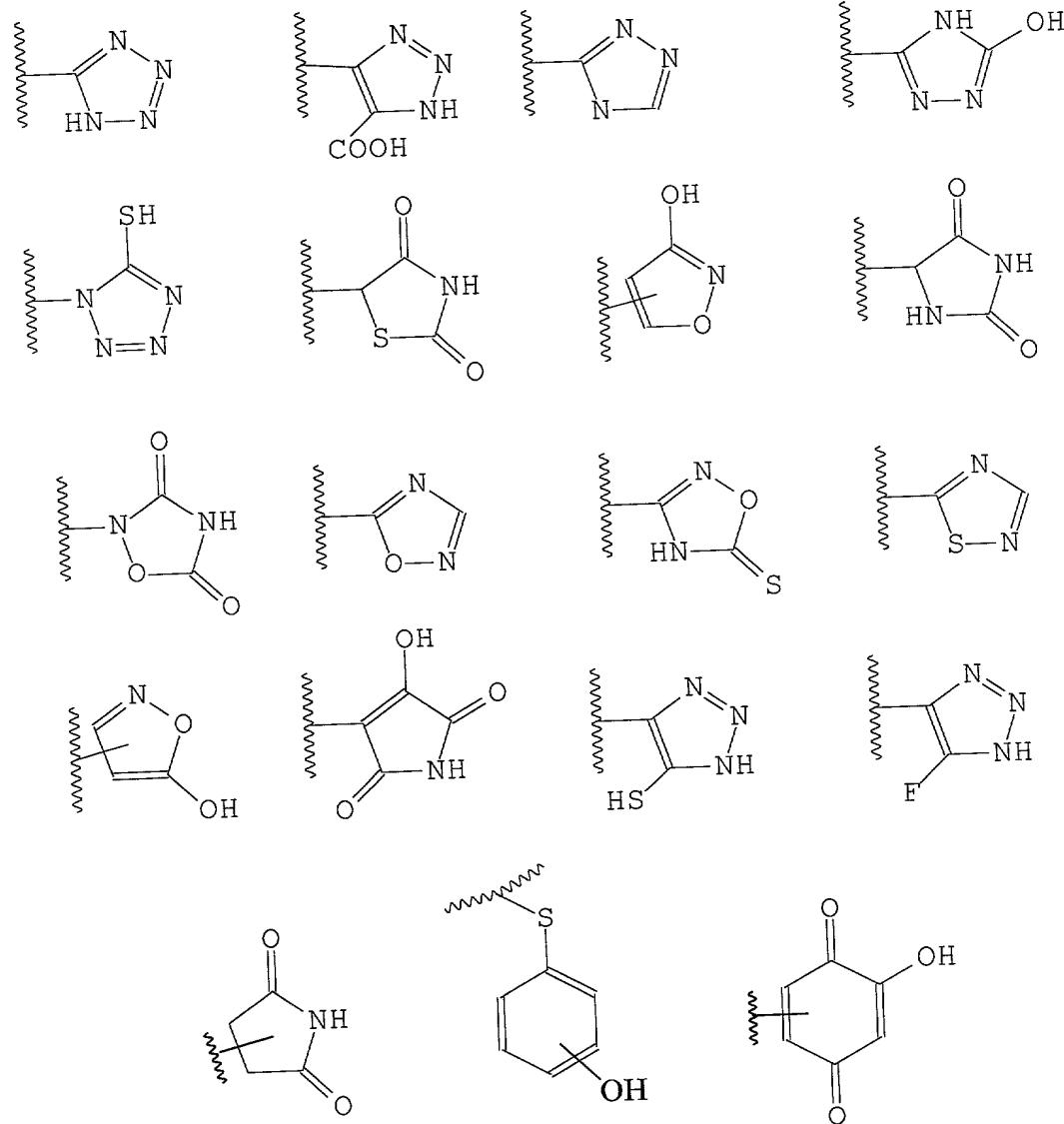
R<sub>2</sub> is a carboxylic acid or a carboxylic acid isostere; wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl,

carbocycle, heterocycle, or carboxylic acid isostere is optionally substituted with one or more substituents selected from R<sup>3</sup>, where

R<sup>3</sup> is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulphydryl, thioalkyl, alkylthio, sulfonyl, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO<sub>2</sub>R<sup>4</sup> where R<sup>4</sup> is hydrogen or C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl or alkenyl; or a pharmaceutically acceptable salt, ester or solvate thereof.

52. The method of claim 51, wherein R<sub>2</sub> is a carbocycle or heterocycle containing any combination of CH<sub>2</sub>, O, S, or N in any chemically stable oxidation state, wherein any of the atoms of said ring structure are optionally substituted in one or more positions with R<sup>3</sup>.

53. The method of claim 51, wherein R<sub>2</sub> is selected from the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R<sup>3</sup>.

5 54. The method of claim 51, wherein R<sub>2</sub> is selected from the group consisting of:

-COOH, -SO<sub>3</sub>H, -SO<sub>2</sub>HNR<sup>3</sup>, -PO<sub>2</sub>(R<sup>3</sup>)<sub>2</sub>, -CN, -PO<sub>3</sub>(R<sup>3</sup>)<sub>2</sub>, -OR<sup>3</sup>, -SR<sup>3</sup>, -NHCOR<sup>3</sup>, -N(R<sup>3</sup>)<sub>2</sub>, -CON(R<sup>3</sup>)<sub>2</sub>, -CONH(O)R<sup>3</sup>, -CONHNHSO<sub>2</sub>R<sup>3</sup>, -COHNSO<sub>2</sub>R<sup>3</sup>, and -CONR<sup>3</sup>CN.

10 55. The method of claim 46, wherein the N-linked sulfonamide of an N-heterocyclic carboxylic acid compound is selected from the group consisting of compounds 1-97.

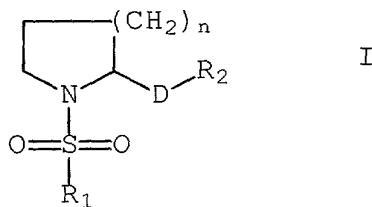
15 56. The method of claim 46, further comprising administering a neurotrophic factor different from formula (I).

20 57. The method of claim 56, wherein said neurotrophic factor different from formula (I) is selected from the group consisting of neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotropin-3, and neurotropin 4/5.

30 58. A method for treating alopecia or promoting hair growth in an animal, which comprises administering to said animal an effective amount of an N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere.

59. The method of claim 58, wherein the N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere is non-immunosuppressive.

5 60. The method of claim 58, wherein the N-linked sulfonamide of an N-heterocyclic carboxylic acid or carboxylic acid isostere is a compound of formula (I):



where

n is 1-3;

R<sub>1</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>9</sub> straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, or heterocycle;

D is a bond, or a C<sub>1</sub>-C<sub>10</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>10</sub> alkynyl;

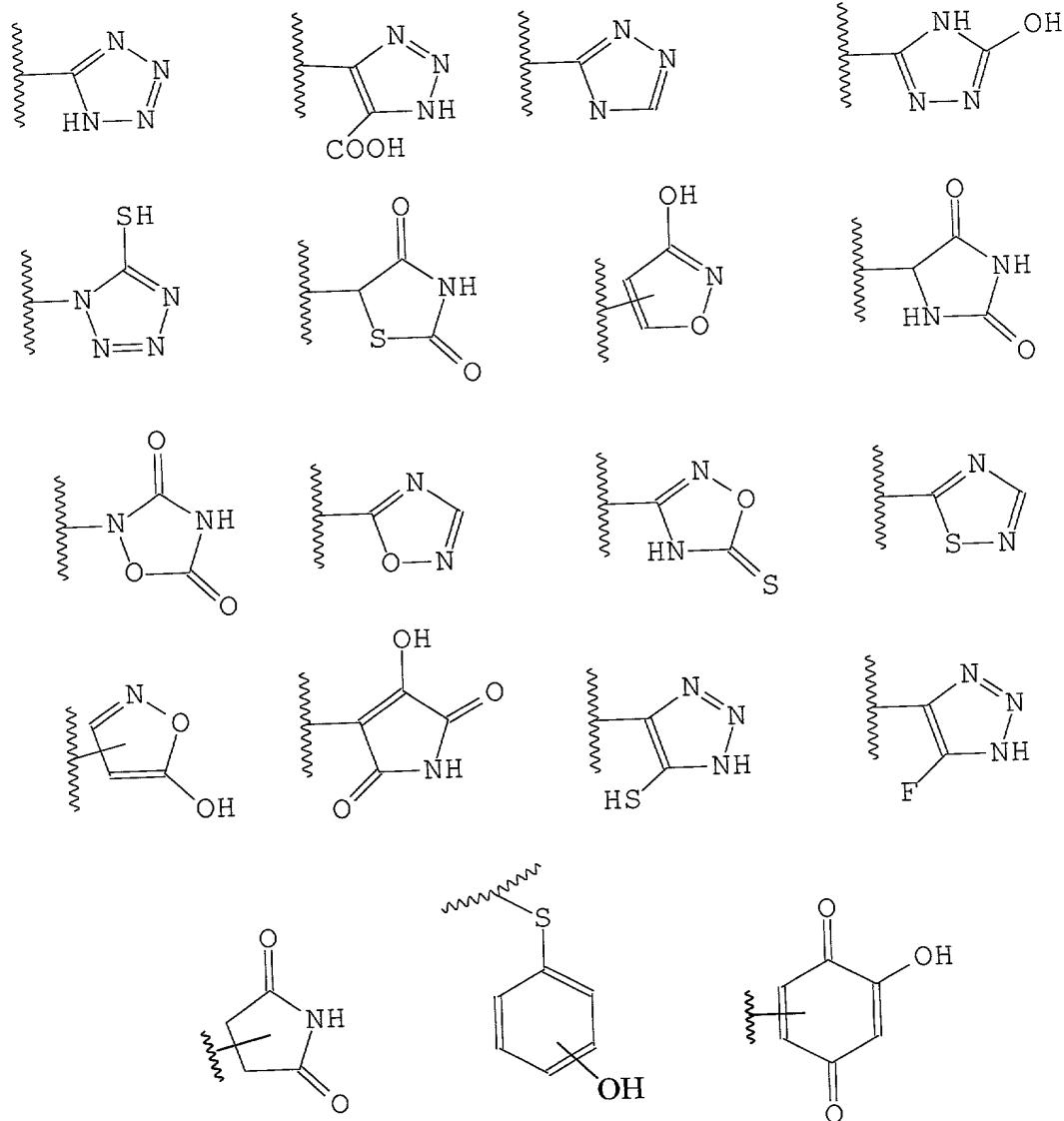
R<sub>2</sub> is a carboxylic acid or a carboxylic acid isostere; wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or carboxylic acid isostere is optionally substituted with one or more substituents selected from R<sup>3</sup>, where

R<sup>3</sup> is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulphydryl, thioalkyl, alkylthio, sulfonyl, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO<sub>2</sub>R<sup>4</sup> where R<sup>4</sup> is hydrogen or C<sub>1</sub>-C<sub>9</sub>

straight or branched chain alkyl or alkenyl;  
or a pharmaceutically acceptable salt, ester or solvate  
thereof.

5       61. The method of claim 60, wherein R<sub>2</sub> is a carbocycle  
          or heterocycle containing any combination of CH<sub>2</sub>, O, S,  
          or N in any chemically stable oxidation state, wherein  
          any of the atoms of said ring structure are optionally  
          substituted in one or more positions with R<sup>3</sup>.

10      62. The method of claim 60, wherein R<sub>2</sub> is selected from  
          the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R<sup>3</sup>.

63. The method of claim 60, wherein R<sub>2</sub> is selected from  
5 the group consisting of

-COOH, -SO<sub>3</sub>H, -SO<sub>2</sub>HNR<sup>3</sup>, -PO<sub>2</sub>(R<sup>3</sup>)<sub>2</sub>, -CN, -PO<sub>3</sub>(R<sup>3</sup>)<sub>2</sub>, -OR<sup>3</sup>, -SR<sup>3</sup>, -NHCOR<sup>3</sup>, -N(R<sup>3</sup>)<sub>2</sub>, -CON(R<sup>3</sup>)<sub>2</sub>, -CONH(O)R<sup>3</sup>,  
-CONHNHSO<sub>2</sub>R<sup>3</sup>, -COHNSO<sub>2</sub>R<sup>3</sup>, and -CONR<sup>3</sup>CN.

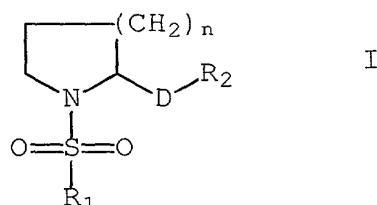
10 64. The method of claim 58, wherein the carboxylic acid  
or carboxylic acid isostere is selected from the group  
consisting of compounds 1-97.

15 65. A pharmaceutical composition comprising:

(i) an effective amount of a N-linked sulfonamide of  
an N-heterocyclic carboxylic acid or carboxylic  
acid isostere for treating alopecia or promoting  
hair growth in an animal; and  
20 (ii) a pharmaceutically acceptable carrier.

25 66. The pharmaceutical composition of claim 65, wherein  
the N-linked sulfonamide of an N-heterocyclic carboxylic  
acid or carboxylic acid isostere is non-  
immunosuppressive.

67. The composition of claim 65, wherein the carboxylic  
acid or carboxylic acid isostere is a compound of  
formula (I):



where

n is 1-3;

R<sub>1</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>9</sub>, straight or branched chain alkyl, C<sub>2</sub>-C<sub>9</sub>, straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, or heterocycle;

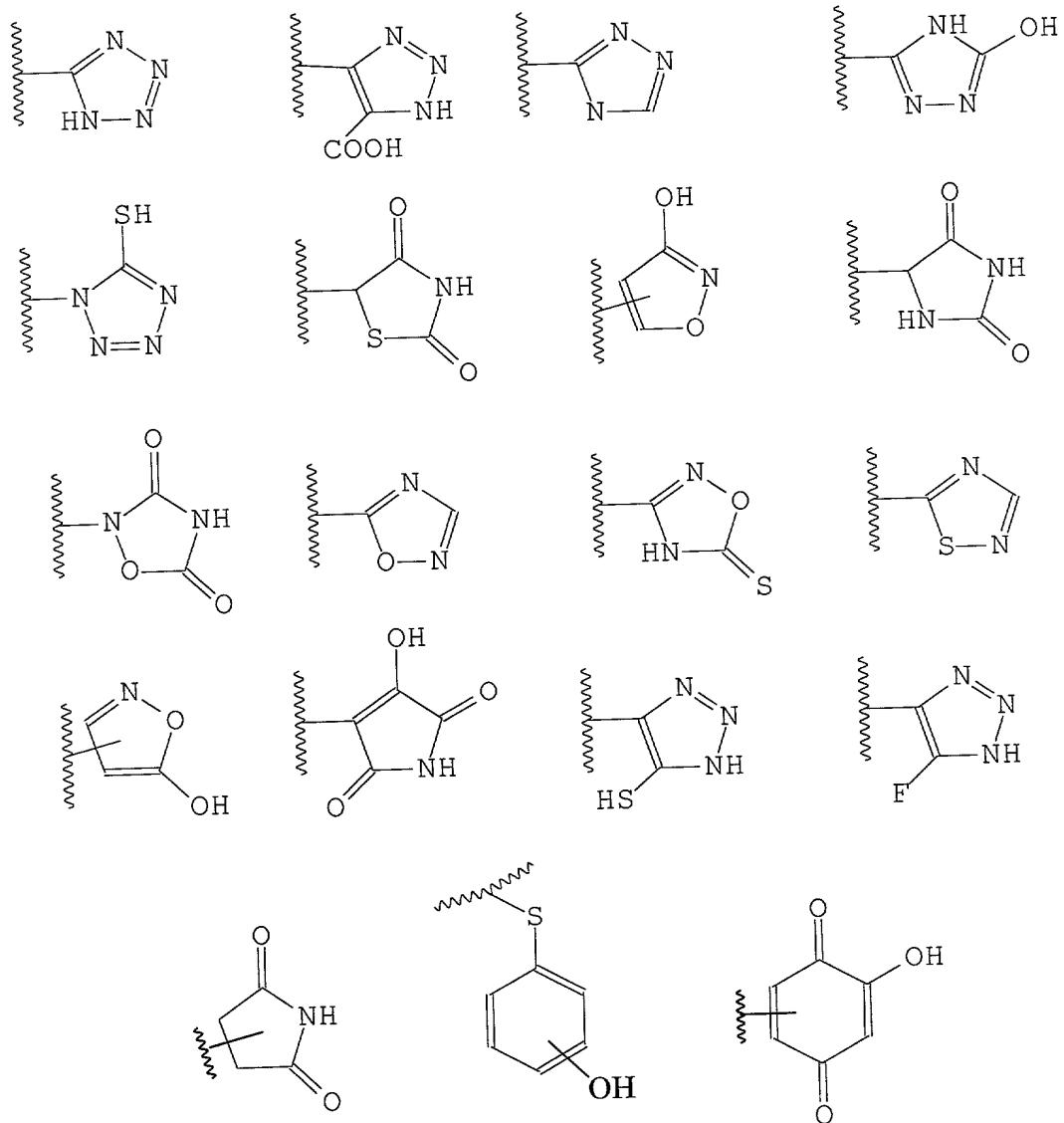
D is a bond, or a C<sub>1</sub>-C<sub>10</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>10</sub> alkynyl;

R<sub>2</sub> is a carboxylic acid or a carboxylic acid isostere; wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or carboxylic acid isostere is optionally substituted with one or more substituents selected from R<sup>3</sup>, where

R<sup>3</sup> is hydrogen, hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulphydryl, thioalkyl, alkylthio, sulfonyl, C<sub>1</sub>-C<sub>6</sub> straight or branched chain alkyl, C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO<sub>2</sub>R<sup>4</sup> where R<sup>4</sup> is hydrogen or C<sub>1</sub>-C<sub>9</sub> straight or branched chain alkyl or alkenyl; or a pharmaceutically acceptable salt, ester or solvate thereof.

68. The composition of claim 67, wherein R<sub>2</sub> is a carbocycle or heterocycle containing any combination of CH<sub>2</sub>, O, S, or N in any chemically stable oxidation state, wherein any of the atoms of said ring structure are optionally substituted in one or more positions with R<sup>3</sup>.

69. The composition of claim 67, wherein R<sub>2</sub> is selected from the following group:



where the atoms of said ring structure may be optionally substituted at one or more positions with R<sup>3</sup>.

70. The composition of claim 67, wherein R<sub>2</sub> is selected from the group consisting of:

5 -COOH, -SO<sub>3</sub>H, -SO<sub>2</sub>HNR<sup>3</sup>, -PO<sub>2</sub>(R<sup>3</sup>)<sub>2</sub>, -CN, -PO<sub>3</sub>(R<sup>3</sup>)<sub>2</sub>, -OR<sup>3</sup>, -SR<sup>3</sup>, -NHCOR<sup>3</sup>, -N(R<sup>3</sup>)<sub>2</sub>, -CON(R<sup>3</sup>)<sub>2</sub>, -CONH(O)R<sup>3</sup>, -CONHNHSO<sub>2</sub>R<sup>3</sup>, -COHNSO<sub>2</sub>R<sup>3</sup>, and -CONR<sup>3</sup>CN.

10 71. The composition of claim 65, wherein the carboxylic acid or carboxylic acid isostere is selected from the group consisting of compounds 1-97.

ABSTRACT OF THE DISCLOSURE

This invention relates to novel N-linked sulfonamides of N-heterocyclic carboxylic acid and carboxylic acid isosteres, their preparation, and use for treating neurological disorders including physically damaged nerves and neurodegenerative diseases, and for treating alopecia and promoting hair growth.

Fig. 1

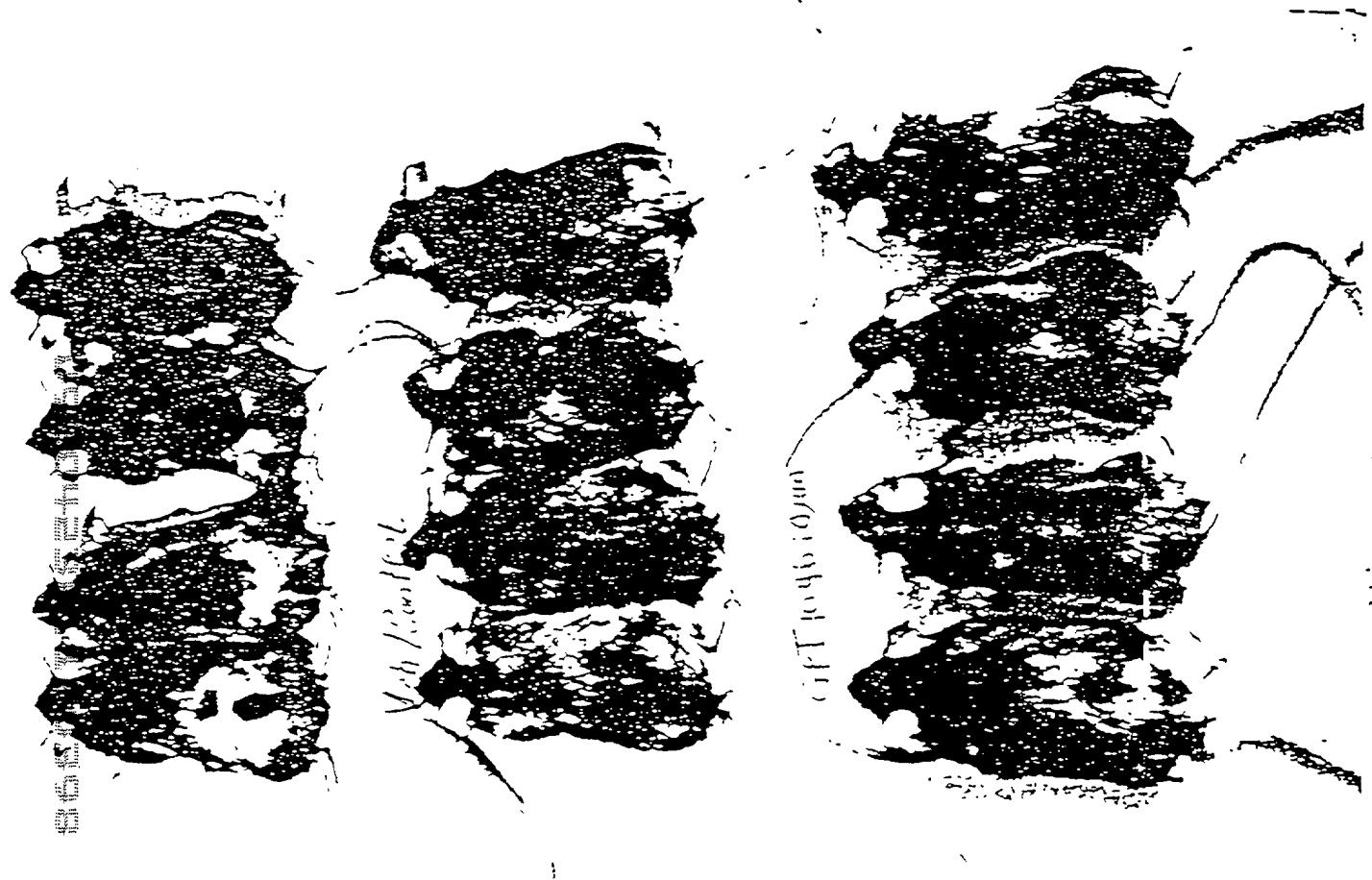
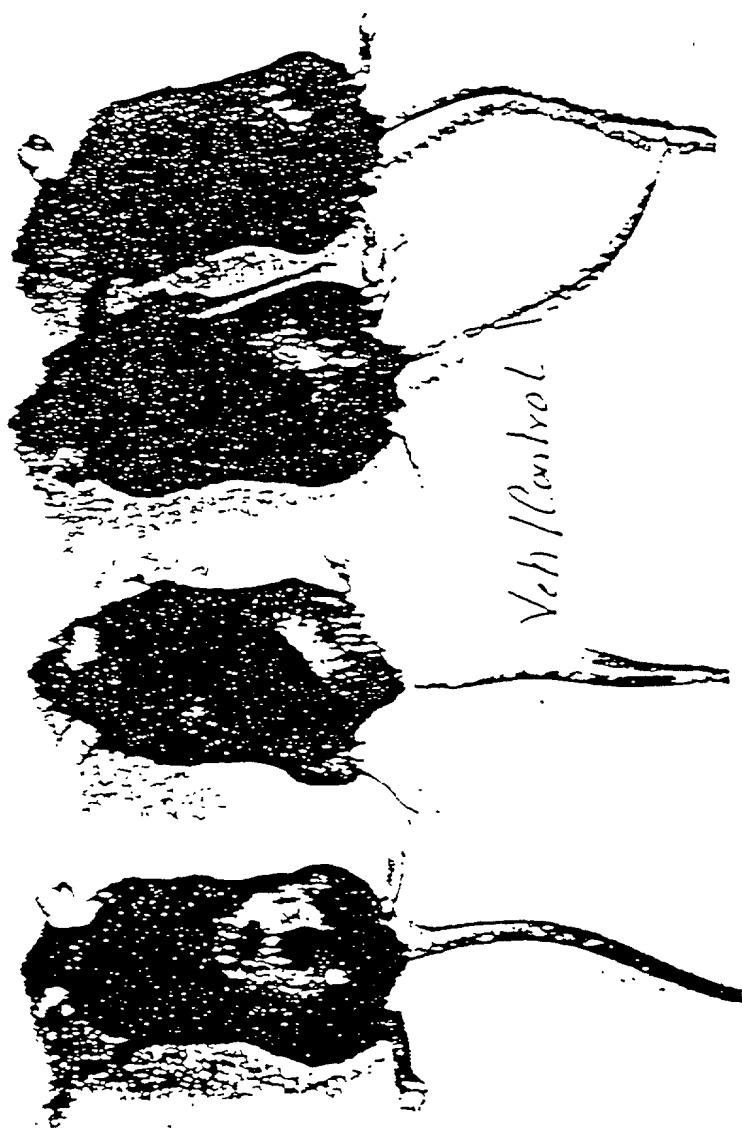
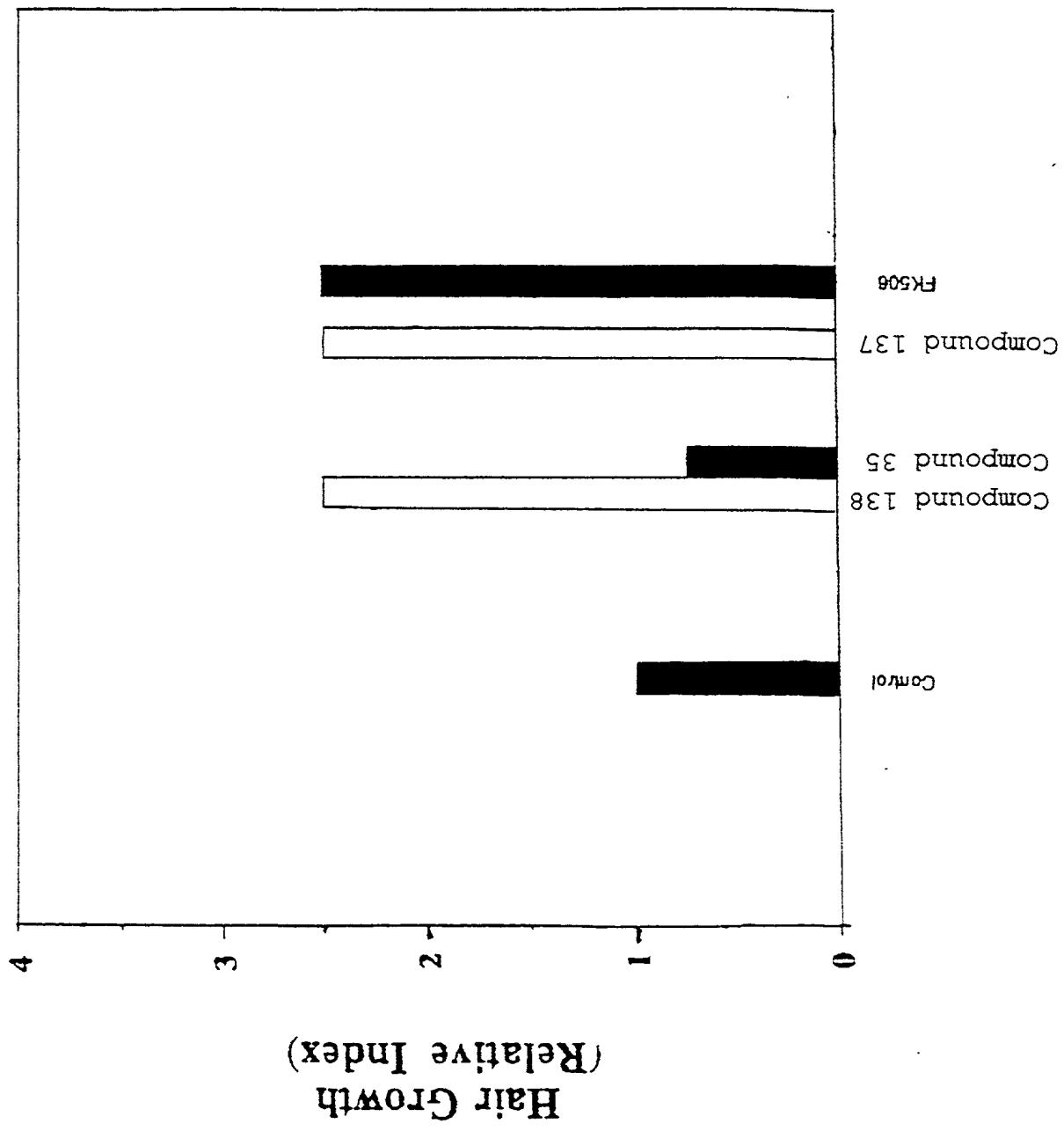


Fig. 2



# Promotion of Hair Growth by Neuroimmunophilin Ligands



**DECLARATION FOR PATENT APPLICATION**

Atty Docket AR218-X

As the below-named inventors, we hereby declare that:

Our residences, post office addresses and citizenships are as stated below next to our name.

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**N-LINKED SULFONAMIDES OF N-HETEROCYCLIC CARBOXYLIC ACIDS AND CARBOXYLIC ACID ISOSTERES**

the specification of which: (check one)

[X] is attached hereto. [ ] was filed on \_\_\_\_\_, as Serial No. \_\_\_\_\_, and was amended on \_\_\_\_\_ 19 (if applicable).

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to the patentability of this application as defined by 37 CFR § 1.56.

We hereby claim foreign priority benefits under 35 U.S.C. § 119 of any foreign application(s) for patent or inventor's certificate listed below, and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Priority Claimed

(Application No.)	(Country)	(Day/Month/Year Filed)	[ ]	[ ]
(Application No.)	(Country)	(Day/Month/Year Filed)	[ ]	[ ]

We hereby appoint Gary M. Nath, Reg. No. 26,965; Irvin A. Lavine, Reg. No. 16,838; Karen Lee Orzechowski, Reg. No. 31,621; Harold L. Novick, Reg. No. 26,011; Suet M. Chong, Reg. No. 38,104; Patricia M. Drost, Reg. No. 29,790; Todd L. Juneau, Reg. No. 40,669; Lee C. Heiman, Reg. No. P-41,827; Donald M. Sandler, Reg. No. 19,237 and Robert G. Lev, Reg. No. 30,280 as our attorneys to prosecute this application and transact all business in the U.S. Patent and Trademark Office connected therewith.

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We hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by 35 U.S.C. § 112, first paragraph, we acknowledge the duty to disclose material information as defined in 37 CFR § 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(U.S. Application Serial No.)	(U.S. Filing Date)	(Status--patented, pending, abandoned)
(U.S. Application Serial No.)	(U.S. Filing Date)	(Status--patented, pending, abandoned)

We hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Inventor's Signature \_\_\_\_\_ Date \_\_\_\_\_

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